Moderate Hyperhomocysteinemia in Patients Treated for Epilepsy

Kolínová M.[1], Dvořáková J.[2], Hladíková E.[3], Preiss J.[4], Hyánek J.[2]
[1]Department of Neurology of the Faculty Policlinic of the First Faculty of Medicine, Charles University in Prague, Czech Republic;
[2]Department of Clinical Biochemistry, Hospital Na Homolce, Prague, Czech Republic;
[3]Institute of Biology and Molecular Genetics of the Second Faculty of Medicine, Charles University in Prague, Czech Republic;
[4]Department of Neurology, Hospital Na Homolce Prague, Czech Republic

Received March 21, 2006, Accepted June 6, 2006

Keywords: Hyperhomocysteinemia – Epilepsy – EEG – Vitamins – Enzymopathy – Antiepileptic drugs

Abbreviations: t Hcy – total plasma homocysteine; Hcy – homocysteine; HHcy – hyperhomocysteinemia; Nudy – t Hcy in normal range; MTHFR – methylen tetra-hydrofolate reductase; AF – acidum folicum; AE – antiepileptic drug; CBZ – carbamazepine; DPH – fenytoin; PR – primidone; PB – phenobarbital; VAL – valproate; L – lamotrigine; PS – partial seizures; SPS – simplex partial seizures; CPS – complex partial seizures; GTCS – generalized tonic clonic seizures; MTS – mesial temporal sclerosis; HLP – hyperlipoproteinemia; US – ultrasound investigation of carotic arteries

Mailing Address: Marie Kolínová, MD., PhD., Department of Neurology of Faculty Policlinic of the First Faculty of Medicine, Charles University, Karlovo náměstí 32, 120 00 Prague 2, Czech Republic, Phone: + 420 224 916 514, e-mail: kolinova.marie@vfn.cz

Abstract: Homocystein (Hcy) is regarded as a neuroexcitatory substance, which is therefore used as an epileptogenic agent in experimental epileptology. Experiments "in vivo" as well as "in vitro" revealed its relation to NMDA glutamate receptors, and its potential neurotoxicity. From the clinical aspect, hyperhomocysteinemia (HHcy), mostly as a marker of the risk factor in the vascular damage, was often studied in patients treated with antiepileptic drugs (AE). However, the neuroexcitatory influence of mild HHcy (up to 30 μmol/l) was rarely discussed. Out of a group of 123 adult patients on long-term conventional AE we analyzed 8 patients (7 men and one woman) with moderate to severe HHcy (30.7–109.0 μmol/l) retrospectively and 2–5 years after HHcy normalization. All of them suffered from partial and/or secondary generalized seizures accompanied by neuropsychological impairment depending on the aetiology of the disease. The patients were characterized by a concurrence of several factors:

1. All of them received conventional AEs inducing the cytochrome P 450 at the time HHcy was diagnosed.
2. Molecular-genetic tests showed enzymopathic impairment (methylentetrahydrofolate reductase – MTHFR mutation of the gene C677 T) also in all eight, homozygous in 7 cases and heterozygous in 1 case.
3. All patients were found to have a vitamin deficit or marginal values of at least one of the vitamins under study, especially folate and/or vitamin B6 and B12. With reference to clinical and EEG features, the potential neuroexcitatory influence of Hcy is discussed taking into account its effect on pathogenetic factors.

Introduction

The problem of hyperhomocysteinemia (HHcy) was reopened in recent years [1], especially in connection with its high-risk nature in respect to vascular diseases [2, 3], and later also in general relations, especially to neuropsychiatry [4] and developmental neurology. The frequent incidence of the mild form of HHcy was confirmed in a number of studies, especially in patients on antiepileptics (AE), e.g., Ono et al., 1997 [5] and Schwaninger et al., 1999 [6] to mention some of the earlier studies, and corroborated by many others in recent years. The results of investigations, including ours, suggest a relation between homocysteine (Hcy) metabolism and the deficit of some vitamins (especially folate, and others, mainly B6, B12) [7, 8, 9]. Genetic studies confirmed the possible incidence of various enzymopathies [10]. As a rule, HHcy is caused by deficit enzyme remethylation or trans-sulphurization reactions in methionine synthesis and degradation where B group vitamins participate as co-factors. Mutation of the gene C677T is demonstrated most frequently (10–15 % population) resulting in the MTHFR deficit (methylentetrahydrofolate reductase) as we could see in our own group of patients [11].

For its neuroexcitatory properties -already in Curtis and Watkins, 1963 [12], Meldrum, 1992 [13], Hcy is used in experimental epileptology as an epileptogenic agent. The Hcy risk in epileptic patients therefore seems notable in many aspects, especially in increased Hcy values. In our work, we evaluated a group of 8 adult patients with moderate to severe HHcy – according to Kang et al., 1987 [14], Malinow, 1994 [15] (values exceeding 30.0 μmol/l). Prospective monitoring was only partially feasible, retrospective evaluation predominated, considering the whole clinical course and the subsequent period following Hcy normalization as a result of vitamin therapy. This raises a question: is the moderate HHcy a random finding without any effect on the disease course or can the change in the clinical course be assumed? If the latter is true, we ought to intensify our search for the persons affected, and not "only" because they are more susceptible to vascular diseases.

Methods and patients

Out of the total of 123 adult patients – 68 men and 55 women – treated at the epilepsy centre with AEs inducing the cytochrome P450 (carbamazepine [CBZ], phenytoin [DPH], phenobarbital [PB], primidone [PR]) – we diagnosed HHcy in about 30 % cases, especially the mild HHcy type – not exceeding 30 μmol/l. The disease was classified as localization-related epilepsy. Moderate HHcy – 30.7–76.0 mmol/l and in one case severe HHcy – 109.0 μmol/l were found between 1998 and 2001 in 8 patients – 7 men and 1 woman.

Tables 1–3 contain the characteristic patients data, in the order of Hcy values. Retrospectively, we described the course of epilepsy using continuous standard EEG and clinical observation, including neuropsychological observation in case studies. The description by the seizure type followed the International League against Epilepsy classification. In some cases, this was complemented with details yielded by objective observation or sporadically by EEG – videomonitoring.

The antiepileptic therapy was conducted according to standard procedures (in respect of the long-term course) including control of AE serum values (not exceeding the so called therapy range), in an effort to minimize any side effects.

The patients were followed up for 30–60 months after Hcy normalization achieved by vitamin therapy – Figure 1. Treatment with vitamins was adapted continuously according to the serum Hcy and vitamin levels (plasma and erythrocyte folate (AF, B6, B12) checks according to our own former experience [16]. The daily doses were as follows: 1 to 5 mg folic acid, 5 to 10 mg vitamin B6 and/or 0.3 mg vitamin B12 per week administered in mono- or combination therapy.

All patients were under comprehensive continuous clinical monitoring including investigations for basic vascular disease risk factors (history, clinical examination, lipid metabolism, ultrasound investigation of carotid arteries [US] – performed on Vigmed Sound).

Total plasma Hcy (tHcy) was assayed using the FPIA immunochemical method on an IMx Abbott apparatus. Plasma folate was determined with the chemiluminiscence method on Imulite; vitamin B6 was ascertained chromatographically (HPLC) on Beckman Gold using Chromosystems Co. sets; B12 – with the MEIA method on an Abbott Axsym. Routine analytical methods including lipid spectrum tests made use of an Synchchron CLX 20 Beckman analyser. Patients suffering from HHcy were differentiated using the L – Methionin loading test [17].

In all 8 patients molecular genetic tests for gene mutation were performed. MTHFR 677C T mutation was found in these patients using a modified analysis according to Frosst et all / PCR amplification and restriction analysis using restriction endonuclease Hinfl [18].

Results

Clinical findings

Clinical and EEG characteristics of patients from the viewpoint of epileptology (Tables 1–3):

Table 1 – Patient characteristics

Patient No.	Age-years Sex	HHcy μmol/l	Aetiology Risk factors	MRI findings	I-seizure -years	Seizure types	AEs (before)	AEs (HHcy)	NHcy μmol/l
1 KB	52 M	30.7	Perinatal para-infectious	None	5	SPS-st epi, GTCS Hypermotor	DPH, CBZ, VALPRIM	PRIM	9.8
2 MR	21 F	36.7	Unknown	None	13	SPS-st epi	CLON CBZ	CBZ	9.1
3 SB	40 M	42.0	Hamartoma	+	10	Hypermotor st epi	DPH, PB, CBZ PRIM	L, VAL	10.1
4 ŽA	44 M	43.1	Fam history	None	10	SPS, CPS hypo, hypermotor	DPH, PB, CBZ	CBZ	12.1
5 TV	65 M	49.7	Posttrau-matic	+	15	SGTCS	DPH, PB, PRIM	PRIM	11.9
6 DL	29 M	58.4	Toxoallergic trauma	MTS	10	SPS, CPS	CBZ, VAL	CBZ	10.6
7 FJ	35 M	76.0	Tumor	Stpparc tu re-section	31	SGTCS sporad	DPH	DPH	9.9
8 VM	29 M	109.0	Perinatal	Cystic lesion atrophy	2	Hemicon-vuls CPS, GTCS	PRIM, CBZ CLON	CBZ CLON	9.4

F – female; M – male; yr – year; HHcy – hyperhomocysteinemia (mmol/l); AEs – antiepileptic drug medication – before and at the time of HHcy determining; NHcy – tHcy value upon vitamin therapy application; MTS – mesial temporal sclerosis; SPS – simple partial seizure; CPS – complex partial seizure; st epi – accumulation of seizures/status epilepticus; GTCS – generalized tonic – clonic seizure; CBZ – carbamazepine; CLON – clonazepam; DPH phenytoin; L – lamotrigine; PB – phenobarbital; PR – primidone; VAL – valproate

Clinical course and retrospective monitoring of EEG findings before HHcy diagnosis: Signs of brain damage were detected in all cases ranging from mild to the severest degree, depending on the aetiology (perinatal 3×, toxoallergic 1×, post-traumatic 1×, mesial temporal sclerosis [MTS] 1×, tumorous 1×, indefinite cryptogenous – 1× – in this case with positive family history of epilepsy, in other cases without a history of epileptic nature).Various types of simple partial seizures (SPS), hypo- as well as hypermotor and complex partial seizures (CPS) and/or secondary generalized seizures (GTCS) – localization-related epilepsy was seen in all patients. The seizure frequency showed marked variations in individual cases, linked to age and different epileptic syndromes, possibly also related to pharmacotherapy, to provoking factors including patient compliance.

All cases were accompanied by neuropsychological impairment, mostly with a normal neurological finding in other aspects, of a more severe degree in 2 cases, with severe organic affection of perinatal aetiology (VM) and in the form of a brain tumour (FJ). As for other parameters considered – such as family history, disease onset, precipitating factors, febrile seizures – these were not clinically characteristic, but male patients strongly predominated.

From the therapeutic point of view, the unifying element lay in the administration of conventional AEs inducing the cytochrome P 450. It may be of interest that from the start of AE administration, 4 patients (KB, SB, ŽA, DL) experienced spells of periods of no improvement or even worsening. However, 2 patients did show improvement together with a prolonged seizure-free period once valproate was started as the dominant therapy.

Repeated EEG investigation – interictal, rarely also ictal in videomonitoring –

Table 2 – EEG characteristics before and after normalization of HHcy

Patient	Fo		GE		HV activation		FS		Background activity	
No.	HHcy	NHcy	HHcy	NHcy	HHcy	NHcy	HHcy	NHcy	HHcy	NHcy
1 KB	+– nepi	–	–	–	–	–	–	–	slightly abnormal	
2 MR	+bi T	+bi T	+nepi	+nepi	+	+	–	–	slightly abnormal	
3 SB	– ict monitor bi F	–	–	–	–	–	–	–	slightly abnormal	
4 ŽA	+– nepi	–	–	–	?	–	–	–	slightly abnormal	
5 TV	+epi	+epi	+epi	+epi	+	++	–	–	slightly abnormal	
6 DL	+nepi	+nepi	+nepi	+nepi	+	+	–	–	slightly abnormal	
7 FJ	+nepi, epi	+nepi	–	–	–	–	–	–	slightly abnormal	
8 VM	+nepi, epi	+nepi, epi	+nepi	+nepi	–	–	–	–	moderately-severely abnormal	

EEG – interictal; Fo – localized or regional abnormality; GE – generalization; HV – hyperventilation activation procedure; FS – photostimulation activation procedure; HHcy – hyperhomocysteinemia; NHcy – tHcy in normal range; epi – epileptiform phenomena; nepi – nonepileptiform phenomena; bi T – bitemporal abnormality; bi F – bifrontal abnormality; ict monitor – ictal EEG videomonitoring

Table 3 – Course of the disease before and after HHcy normalization based on case studies 1–8

Patient No.	Before HHcy normalization	After HHcy normalization
1 KB	Secondary education, single, ID from age of 44, treated from the age of 13, worsening with CAE therapy, improvement with VAL (intolerance-ex), tendency to PS accumulation – st. epilepticus Neuropsychol. weakening, anxious depression sy, non-uniform cognitive functions, memory functions slightly below average, cardiovascular risks – none C677T mutation on both MTHFR gene alleles	Lasting incidence of overnight seizures (GTCS, hypermotoric, 1–4/month), daily PS with accumulation Neuropsychology – no substantial change, psychosocial improvement EEG unchanged NHcy in vitamin therapy by the combination AF, B12, B6
2 MR	Primary education, single, childless, attempt at suicide at the age of 17 (failure at school), treated from the age of 19, VAL intolerance, tendency to accumulation Neuropsychol. weakening – reduced cognitive ability towards less than average, defective level of memory functions, no cardiovascular risks C677T mutation on both MTHFR gene alleles	PS incidence of irregular fr – up to 3 months long intervals Neuropsychol. – no substantial change, psychosocial improvement EEG unchanged NHcy in vitamin therapy by AF, B6
3 SB	Tertiary education, married, 2 children, treated from the age of 10, worsening with CAE therapy, improvement with L, VAL therapy Neuropsychol. weakening – cognitive – including memory tests average, weaker in respect of the education achieved, cardiovascular risks – none C677T mutation on both MTHFR gene alleles	Permanent PS incidence – (hypermotoric) with fr stabilization – several/month – change of medication, VAL intolerance Neuropsychology – no substantial change in the cognitive function, improved only a memory subtest, psychosocial worsening EEG unchanged NHcy in vitamin therapy by AF
4 ŽA	Secondary education, married, 2 children, FH – sister treated for epilepsy; treated from the age of 10, not improved with CAE therapy, tendency to PS accumulation, GTCS Neuropsychology – cognitive – including memory tests average, cardiovascular risks – type II DM in both parents, smoker, US – stenosis ACI bilat. up to 30%, HLP on a diet C677T mutation on both MTHFR gene alleles	Improvement of overnight PS with lower fr and weaker intensity allowing for therapy reduction Neuropsychology – not changed substantially, subjective improvement – more calm EEG unchanged or slightly improvement NHcy in vitamin therapy by AF, B6

5 TV	Tertiary education, researcher, married, childless, treated from the age of 15, rare seizures, no seizures from the age of 48 Neuropsychology – intelligence tests highly above average, memory slightly reduced, especially non-verbal, sporadic marked deficits in the subtest of tactile perception and memory; cardiovascular risks – FH + (father + 53 y i.m.), US – slightly increased resistance without stenosis,angiopathia retinae, changes according to MRI C677T mutation on one MTHFR gene allele	Remains without seizures with maintenance therapy Neuropsychology – no substantial change EEG – focal as well as generalized S, SWC, discharges activated by HV prevails – enhanced in repeated examination NHcy in vitamin therapy by AF, B6 – in the disease course + B12 supplementation
6 DL	Secondary education, single, treated from the age of 15, with progression despite CAE therapy, temporary improvement with VAL therapy, seizure provoked in febrile conditions Neuropsychology – non-uniform cognitive functions, intellect above average to average, memory up to lower average, cardiovascular risks FH +(father + 68 yrs i.m., condition after repeated i.m from 60 yrs), US – normal, HLP with therapy C677T mutation on both MTHFR gene alleles	In the first 2 years in NHcy less frequent PCS (1× per month), later up to 5/month Neuropsychology – no substantial change (current AEs preclude evaluation) EEG improvement only temporary NHcy in vitaminotherapy by AF – in the clinical course + B6, B12 supplementation
7 FJ	Secondary education, single, childless, ID, treated from the 1st seizure in relation with i.c. tumor diagnosis, rare GTCS incidence Neuropsychol. examination – intellect corresponds with the lower average, memory deterioration; cardiovascular risks – smoking, HLP on diet C677T mutation in both MTHFR gene alleles	Condition still without seizures even upon AE reduction Neuropsychology – no substantial change EEG improvement even upon AE reduction NHcy in vitaminotherapy by AF
8 VM	Special school for the sightless, single, ID, treated form childhood, fr. variable, hemiconvulsion up to the age of 11, PS from the age of 15 up to 8–12/month Neuropsychology – idiocy Cardiovascular risks – FH +, HLP on diet C677T mutation on both MTHFR gene alleles	Seizure fr – difficult to evaluate, weaker intensity – improved, psychical condition slightly improved – more calm EEG unchanged NHcy in vitaminotherapy by AF, B12, B6

PS – partial seizure; SPS – simple partial seizures; CPS – complex partial seizures; GTCS – generalized tonic clonic seizures; fr – frequency of seizures; CAE – conventional antiepileptic; VAL – valproate; AF – acidum folicum; B6, B12 – vitamin B6, B12; US – ultrasound investigation of carotid arteries; HLP – hyperlipoproteinemia; FH – family history; i.m. – myocardial infarction

provided evidence of regional lesions and/or paroxysmal manifestations of a secondarily generalized nature with slow waves. In a unique case (TV) the finding was accompanied interictally by bilateral synchronous sharp waves, spikes (S), atypical spike-wave complexes (SWC), discharges with bilateral generalization, activated by hyperventilation. This pattern of paroxysmal abnormality was not noted in other cases, although the patients were monitored regularly and repeatedly at our department on a long-term basis, with at least one EEG examination yearly. In 2 cases only mild diffusely abnormal records were found (in patients with mostly overnight seizures – KB, ŽA); regional or possibly also paroxysmal abnormalities had been described at a younger age.

Comparison of the clinical course and EEG findings before and after HHcy normalization: These are patients with mild to moderate epilepsy in terms of seizure rate, while in 2 cases the patients' condition was not marked by epileptic seizures in comparable periods before and after normalization (TV, FJ). In one case, the rate and intensity of partial nocturnal attacks improved (ŽA), in other cases, after Hcy normalization, the patients' condition showed no detectable change in seizure frequency, while the nature of the seizures remained the same or could not be evaluated since the comparable period was achieved without

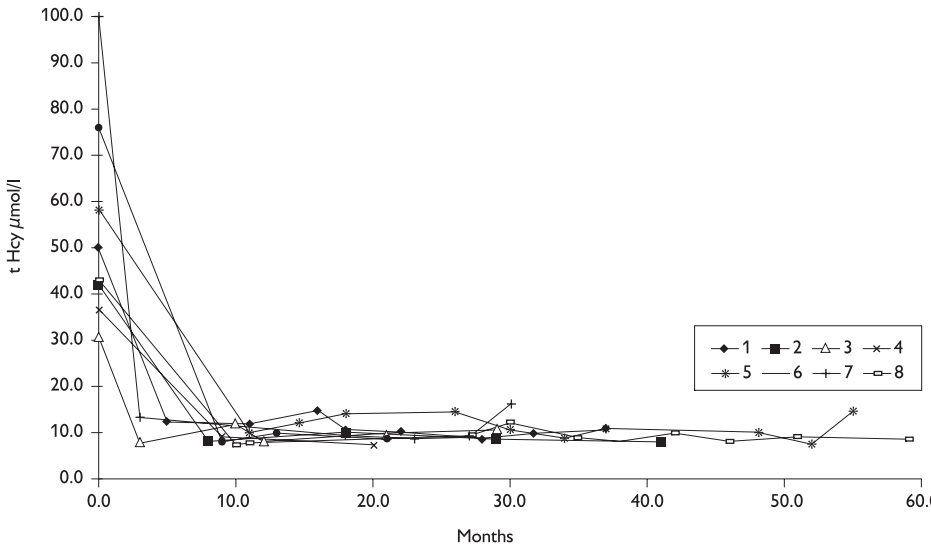

Figure 1 – t Hcy before and after vitaminotherapy (n=8); tHcy values measured in patients 1–8 at the time of first HHcy determining and continuous measurements in the subsequent period with vitamin therapy; the rate of NHcy achievement depended on the vitamin therapy timing; t Hcy – total plasma homocysteine; HHcy – hyperhomocysteinemia

changing the medication. The MTS patient worsened after 2 years – the rate of CPS-type seizures increased (DL).

EEG examinations showed attenuation of localized epileptic discharges in one case (FJ), in others, where regional component prevailed, it did not change substantially (Table 2). EEG findings differed from each other concerning the degree or characteristic features: only mild abnormalities interictally in 3 cases (KB, ŽA, SB), moderate to severe in others. Generalized abnormality with bilateral synchronous S, SW discharges was an accompanying pattern in one patient only (TV), while the focal component was present as well – see Figure 2. In keeping with this figure, this abnormality type persisted markedly after Hcy normalization under comparable conditions, with no change of medication (the patient was stabilized clinically on a long-term basis, with primidon as maintenance medication).

Neuropsychological monitoring was performed in 7 patients (in the VM patient no comparison was possible). Although in some parameters an improvement was found and none worsening was seen in any one case (Table 3), non-prospective observation does not allow more detailed comparison. According to

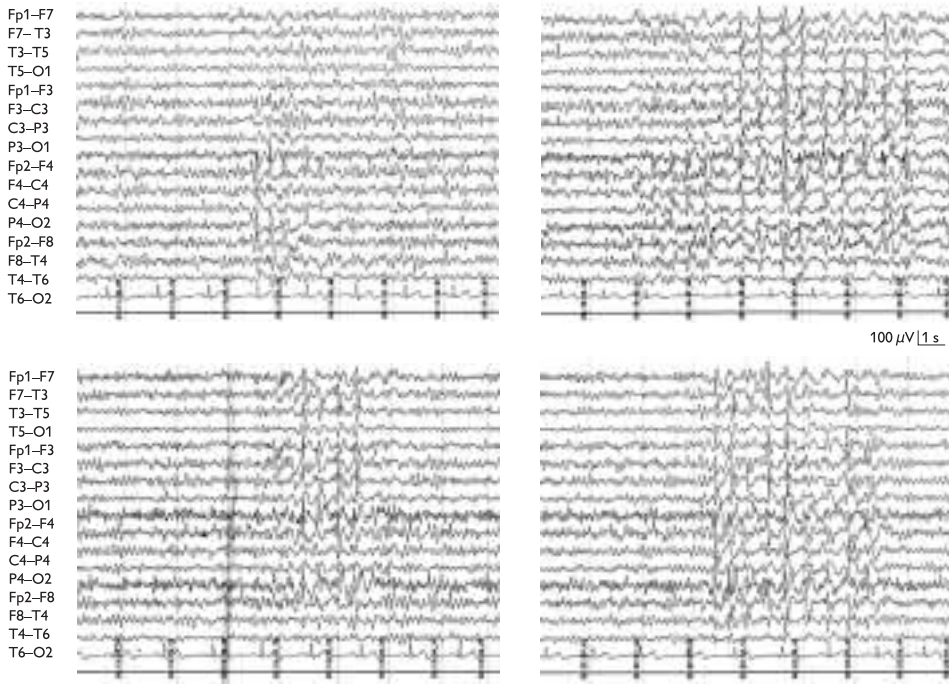

Figure 2 – Interictal EEG. Up – Characteristic seizure pattern before HHcy normalization; Bellow – Characteristic seizure pattern after HHcy normalization; Left – Characteristic sample before hyperventilation; Right – activation by hyperventilation (4 minutes). Comparable samples of both graphs.

comprehensive clinical practice assessment, no substantial changes occurred in any of the patients that could be examined.

Other biological findings

Vitamin therapy – Vitamin deficiency was a frequent finding. In terms of HHcy influence, vitamin therapy showed long-lasting efficacy (Figure 1). According to individually controlled medication results, low doses suffice to achieve Hcy normalization. Although folate supplementation was most effective, in 6 cases it was accompanied by vitamin B6 deficiency and, less frequently, also by vitamin B12 deficiency. B12 and/or B6 deficiency was found associated from the beginning of monitoring , or during the subsequent period in relation to treatment with folate (Table 3). Findings published earlier for a wider group of our patients suffering from mild HHcy were in agreement.

Vascular risk factors – Monitoring for vascular damage risk factors revealed co-incidence with mild hyperlipidemia (HLP) in 5 cases including one case (ŽA) with evident US changes in the carotids. In a 68-year old patient, multi-focal CT and MRI changes in the brain parenchyma were diagnosed as being of vascular aetiology. Positive risk factors for vascular damage or amount of risk were found in 4 cases. In 3 cases, no vascular damage risk factors were found in any of the parameters under scrutiny. Clinical rating of HHcy as an independent vascular risk factor ought to be considered.

Molecular genetic examination – Molecular genetic investigation demonstrated a mutation of the gene for MTHFR in all 8 patients. 677CT mutation linked to both alleles was found in 7 patients and to one allele in one patient.

Discussion

HHcy is viewed as an ecogenetic problem and recommendations for problem groups examination (mostly cardiovascular, neurodegenerative impairments, pregnancy complications) or even screening (of elderly and newborns) are published, though there are some unresolved questions [1].

HHcy was often studied in patients treated for epilepsy with markedly more frequent HHcy incidence than in common population. In relation to our previous results in 82 patients, we analyzed patients with the highest values measured, i.e. above 30 umol/l in the s.c. moderate HHcy zone, considering especially the possibility of homocystein epileptogenicity. Moderate HHcy was connected with the MTHFR 677TT genotype finding in all the 8 patients in the classical AEs therapy, together with a vitamin deficit. It can be thus assumed that these main factors participate in the incidence of metabolic disorders. The predominance of men is high and remains unexplained, although the higher HHcy incidence in men is known (however, the gender differences become balanced in the adult age).

In clinical practice Hcy is known as a substance with an epileptogenic effect in inborn homocysteinuria, with high Hcy values above 100 mmol/l; the effect of mild

and moderate HHcy is not discussed anywhere in literature. However, recent clinical and experimental studies suggest the role of homocystein metabolism and its defects in the neural plasticity and neurodegenerative disorders [4] also in relation to mild HHcy. The relation to glutamate receptors was revealed in experiments "in vitro" as well as "in vivo" [19–21]. The nervous system sensitivity can result in neuroexcitability changes and/or neurotoxicity. Both mechanisms could be taken into account in pathogenesis of the nervous system disorders, also in epilepsy. A marked neurogenic exciting effect of Hcy was already experimentally demonstrated in the 1960s [12] and homocysteine is still used in experimental models, especially in the study of status epilepticus in rodents. It has been known since the earliest studies, especially thanks to Folbergrová,who identified Hcy effects in 1974 [22] for the first time and later also in studies with adult and developing rodents [23–26]. The homocysteic acid model has been recently frequently used; the homocysteic acid – an oxidative product of homocysteine – also has a marked neuroexcitatory effect [13, 27]. In this model, seizures were prevented by group III metabotropic glutamate receptor agonists.

Clinical monitoring can hardly be compared with experimental models, methodological situations are scarcely comparable. Observation of patient described upon moderate HHcy decrease do not provide evidence of a strong HHcy effect, hidden action cannot be excluded. Our observation may invoke hypothetic considerations only. In all cases described in the present study, our patients condition was stabilized already, more or less controlled with AEs. Conventional antiepileptics used in the experimental model described by Walton and Treiman, 1988 [28], proved efficacious in response to the Hcy derivative – homocysteine thiolactone – in combination with cobalt focus in rats [29, 30]. It macany be discussed whether HHcy, in connection with the focal component can play the role of a modulatory factor in the pathogenesis of some epileptic syndromes. All of the 8 patients described suffered from partial epilepsy and a long-term effect of HHcy or disposition to HHcy can be assumed (MTHFR enzyme deficiency in connection with the drug effect on a long-term basis). The synergistic effect has been described in mild HHcy and this effect has been observed also in increased levels [31–35].

From the therapeutical point of view, it may be of an interest that in 4 patients presented in this paper, periods with no improvement or even worsening prevailed in the course of the disease from the beginning of treatment with inducer-type AE medication. However, in two of them improvement was seen after valproate adminnistration as the dominant therapy. In this respect, it is possible to ask how important the therapy is for HHcy with consequences, as unlike other groups of patients, the valproate group was found to have a significantly lower tHcy, and HHcy in sporadic cases only [33]. The findings reported in literature often concur with ours [32–35], in other cases there is no

difference between CBZ- or VAL-treated children, on the contrary [36, 37]. One of the possible explanations of different findings lies in the different approach to pharmacotherapy, and/or in that the differences are related to other factors, including aetiopathogenesis or metabolism.

The lack of improvement after Hcy normalization or, indeed, worsening of the generalized type of EEG abnormality with bilateral synchronous epileptiform discharges, S, atypical SWC, activated by hyperventilation (TV – Figure 2) may suggest a differentiated – if any – Hcy neuroexcitatory influence, differentiated in individual cases according to the aetiopathogenesis. In this case, the Hcy decline from 49.7 mmol/l to normal values failed to improve the abnormality promptly enough or induce long-term improvement (up to 3 years). It can only be speculated about the possibility of different HHcy action on individual aetiopathogenesis components in respect to the finding sporadicity. A different HHcy effect on focal and generalized abnormalities cannot be excluded. The possible neuroexcitatory effect of folic acid should also be taken into account [38]. Nevertheless it does not seen probable due to regularly provided control levels (of plasma and erythrocyte folate), as well due to our own experience. The above described abnormality in the presented case (TV) was found before the folic acid administration. From the vitamin therapy point of view, its monitoring appears to be clinically significant to avoid overdosages with possible interactions of vitamin metabolisms.

The inconclusive nature of the marked epileptogenic effect of HHcy in our group is in line with our formerly presented findings in patients with regard to the L – Methionine test. In this group, clinical as well as EEG follow-up of 12 patients with short-term invoked moderate HHcy (48–109 mmol/l) never showed any clinical or EEG worsening of epileptic manifestations either [39]. But again it is necessary to bear in mind that these studies are performed while the patients are on AE as well as they have vitamin supplementation.

From the neuropsychological point of view, all these cases involved cognitive weakening, and especially the memory component weakening. According to the above mentioned studies, Hcy influence can't be excluded. As for neurodegenerative diseases, especially of the dementia type, HHcy can also be suspected as a possible risk factor. In this context, vitamin deficiency may act synergically [40–42, 4].

Conclusion

There are many aspects which ought to be taken into account with homocystein metabolism in epileptic patients. The small number and partly retrospective observations do not allow making any definite conclusion concerning the neuroexcitatory effect of HHcy in clinical conditions. However the importance of HHcy during AE therapy in relation to other risks and monitoring of vitamin therapy ought to be taken in mind.

References

1. REFSUM H., SMITH A. D., UELAND P. M., NEXO E., CLARCE R., MC PARTLIN J., JOHNSTON C., ENGBAEK F., SCHNEEDE J., MC PARTLIN C., SCOTT J. M.: Facts and recommendations about total homocysteine determinations: An expert opinion. *Clin. Chem.* 50: 3–32, 2004.
2. NYGARD O., VOLSET S. E., REFSUM H., BRATTSTROM L., UELAND P. M.: Total homocysteine and cardiovascular disease. *J. Intern. Med.* 246: 425–54, 1999.
3. DE BREE A., VERSCHUREN W. A. M., KROMHOUT D., KLUJTMANS L. A. J., BLOM H. J.: Homocysteine determinants and the evidence to what extent homocysteine determines the risk of coronary heart disease. *Pharmacol. Rev.* 54: 599–618, 2002.
4. MATTSON M. P., SHEA T. B.: Folate and homocysteine metabolism in neural plasticity and neurodegenerative impairments. *Trends in Neurosciences* 26: 1–10, 2003.
5. ONO H., SAKAMOTO A., EGUCHI T., FUJITA N., NOMURA S., UEDA H., SAKURA N., UEDE K.: Plasma total homocysteine concentrations i epileptic patients taking anticonvulsants. *Metabolism* 46: 959–962, 1997.
6. SCHWANINGER M., RINGLEB P., WINTER R., KOHL B., FIEHN W., RIESER P. A., WALTER-SACK I.: Elevated plasma concentrations of homocysteine in antiepileptic drug treatment. *Epilepsia* 40: 345–350, 1999.
7. SLAVIK M., SMITH K. J., BLANC O.: Decrease of serum pyridoxal phosphate levels and homocysteinemia after administration of 6-azauridine triacetate and their prevention by administration of pyridoxine. *Biochem. Pharmacol.* 31: 4089–4092, 1982.
8. HYÁNEK J., STŘÍBRNÝ J., ŠEBESTA P. ET AL.: Hyperhomocysteinemia: A risk factor for the development of vascular diseases not associated with lipid levels. *Čas. Lék. Čes.* 136: 720–723, 1997.
9. KOLÍNOVÁ M., DVOŘÁKOVÁ J., HYÁNEK J.: Characteristics of epileptic patients with hyperhomocysteinemia.*Čs. Neurol. Neurochir.* 64: 16–21, 2001.
10. KOŽICH V., KRAUS J., HYÁNEK J.: Homocysteine, genes, vitamins: Cardiovascular diseases and complications in pregnancy. *DMEV* 3: 113–120, 1999.
11. DVOŘÁKOVÁ J., KOLÍNOVÁ M., HLADÍKOVÁ E., HYÁNEK J.: Hyperhomocysteinemia in patients on antiepileptic drugs- relation to the mutation in the methylentetrahydrofolate reductase gene. Euromedlab V, Praha /Abstracts/, 2001.
12. CURTIS D. R., WATKINS J. C.: Acidic aminoacids with strong excitatory actions on mammalian neurones. *J. Physiol. (*London) 66: 1–4, 1963
13. MELDRUM B. S.: Excitatory amino acids in epilepsy and potential novel therapies. *Epilepsy Res.* 12: 189–196, 1992.
14. KANG S. S., WONG P. W. K., NORUSIS M.: Homocysteinemia due to folate deficiency. *Metabolism* 36: 458–462, 1987.
15. MALINOW M. R.: Homocysteine and arterial occlusive disease. *J. Intern. Med.* 236: 603–609, 1994.
16. DVOŘÁKOVÁ J., KOLÍNOVÁ M., HYÁNEK J., TÁBORSKÝ L.: Vitamin supplementation in epileptic patients with hyperhomocysteinemia. Abstract. XIIth International Symposium on Atherosclerosis, Stockholm, Sweden, June 25–29, 2000.
17. HYÁNEK J., PEJZNOCHOVÁ H., DVOŘÁKOVÁ J. ET AL.: Our experience in mild hyperhomocysteinemia differentiating. *Klin. Biochem. Metab.* 8:, 58–62, 2000.
18. FROSST P., BLOM H. J., MILOS R., GOYETTE P., SHEPPARD C. A., MATTHEWS R. G., BOERS G. J. H., DEN HEIJER M., KLUIJTMANS L. A., VAN DER HEUVEL L. P., ROZEN R.: A candidate genetic risk factor for vascular disease: a common mutation in methylentetrahydrofolate reductase. *Nat. Genet.* 10: 111–113, 1995.

19. LIPTON S. A., KIM W. K., CHOI Y. B., KUMAR S., D'EMILIA D. M., RAYUDU P. V., ARNELLE D. R., STAMLER J. S.: Neurotoxicity associated with dual actions of homocysteine at the N-methyl-D- aspartate receptor. *Proc. Natl. Acad. Sci. U. S. A.* 94: 5923–5928, 1997.
20. KRUMAN I. I., CULMSEE C., CHAN S. L., KRUMAN Y., GUO Z., PENIX L., MATTSON M. P.: Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersenzitivity to excitotoxicity. *J. Neurosci.* 20: 6920–6926, 2000.
21. LANGMEIER M., FOLBERGROVÁ J., HAUGVICOVÁ R., POKORNÝ J., MAREŠ P.: Neuronal cell death in hipopocamus induced by homocysteic acid in immature rats. *Epilepsia* 44: 299–304, 2003.
22. FOLBERGROVÁ J.: Energy metabolism of mouse cerebral cortex during homocysteine convulsions. *Brain. Res.* 81: 443–454, 1974.
23. MAREŠ P., PAYNE J., FISCHER J.: The electrographic pattern of homocysteine-induced seizures in the rat. *Physiol. Bohemoslov.* 25: 427–429, 1976.
24. KUBOVÁ H., FOLBERGROVÁ J., MAREŠ P.: Seizures induced by homocysteine in rats during ontogenesis. *Epilepsia* 36: 750–756, 1995.
25. FOLBERGROVÁ J.: Anticonvulsant action of both NMDA and non-NMDA receptor antagonists against seizures induced by homocysteine in immature rats. *Exp. Neurol.* 145: 442–450, 1997.
26. MAREŠ P., FOLBERGROVÁ J., LANGMEIER R., HAUGVICOVÁ R., KUBOVÁ H.: Convulsant action of D,L-homocysteic acid and its stereoisomers in immature rats. *Epilepsia* 38: 767–776, 1997.
27. FOLBERGROVÁ J., HAUGVICOVÁ R., MAREŠ P.: Seizures induced by homocysteic acid in immature rats are prevented by group III metabotropic glutamate receptor-agonist /R,S/-4-phosphonophenylglycine. *Exp. Neurol.* 180: 46–54, 2003.
28. WALTON N. Y., TREIMAN D. M.: Experimental secondarily generalized convulsive status epilepticus induced by D,L-homocysteine thiolactone. *Epilepsy Res.* 2: 79–86, 1988.
29. WALTON N. Y., TREIMAN D. M.: Valproic acid treatment of experimental status epilepticus. *Epilepsy Res.* 12: 199–205, 1992.
30. WALTON N. Y., TREIMAN D. M.: Lamotrigine vs. Phenytoin for treatment od status epilepticus: comparison in an experimental model. *Epilepsy Res.* 24: 19–28, 1996.
31. APELAND T., MANSOOR M. A., STRANDJORD R. E., VEFRING H., KRISTENSEN O.: Folate, homocysteine and methionine loading in patients on carbamazepine. *Act. Neurol. Scand.* 103: 294–299, 1999.
32. YOO J. H., HONG S. B.: A common mutation in the methylenetetrahydrofolate reductase gene is a determinant of hyperhomocysteinemia in epileptic patients receiving anticonvulsants. *Metabolism* 48: 1047–1051, 1999.
33. DVOŘÁKOVÁ J., KOLÍNOVÁ M., HYÁNEK J., KRYŠTŮFKOVÁ O., TICHÁ J.: Hyperhomocysteinaemia in patients on anticonvulsants – initial experience. *Klin. Biochem. Metab.* 3: 190–97, 2000.
34. APELAND T., MANSOOR M. A., STRANDJORD R. E., KRISTENSEN O.: Homocysteine concentrations and methionine loading in patients on antiepileptic drugs. *Acta Neurol. Scand.* 101: 217–223, 2000.
35. GIDAL B. E., TAMURA T., HAMMER A., VUONG A.: Blod homocysteine, folate and vitamin B-12 concentrations in patients with epilepsy receiving lamotrigine or sodium valproate for initial monotherapy. *Epilepsy Res.* 64: 161–166, 2005.
36. VERROTTI A., PASCARELLA R., TROTTA D., GIUVA T., MORGESE G., CHIARELLI F.: Hyperhomcysteinemia in children treated with sodium valproate and carbamazepine. *Epilepsy Res.* 41: 253–257, 2000.

37. KARABIBER H., SONMEZGOZ E., OZEROL E., YAKINCI C., OTLU B., YOLOGLU S.: Effects of valproate and carbamazepine on serum levels of homocysteine, vitamin B 12, and folic acid. *Brain and Development* 25: 113–115, 2003.
38. VAN RIJN C. M., VAN DER VELDEN T. J. A. M., RODRIGUES DE MIRANDA J. F., FEENSTRA M. G. P., HIEL J. A. P., HOMMWA O. R.: Folates: epileptogenic effects and enhancing effects on [H] TBOB binding to the GABA a – receptor complex. *Epilepsy Res.* 5: 199–208, 1990.
39. KOLÍNOVÁ M., DVOŘÁKOVÁ J., HYÁNEK J.: Homocysteine and epilepsy. Initial experiences. XVII.slovenský a český Neurologický zjazd, XIII.slovenský a český epileptologický zjazd a XXVIII. Reimanove Dni, Prešov 2000.
40. SCHMITZ B.: Psychiatric syndromes related to antiepileptic drugs. *Epilepsia* 40 (Suppl 10): 65–70, 1999.
41. BOTTIGLIERI T., PARNETTI L., ARNING E., ORTIZ T., AMICI S., LANARI A., GALLAI V.: Plasma total homocysteine levels and the C677T mutation in the methylenetetrahydrofolate reductase / MTHFR/ gene: a study in an Italian population with dementia. *Mechanisms of Ageing and Development* 122: 2013–2339, 2001.
42. ZHU B. T.: On the mechanism of homocysteine pathophysiology and pathogenesis: a unifying hypothesis. *Histol. Histopathol.* 17: 1283–1291, 2002.