

THROMBOTIC ISCHEMIC STROKE IN A CASE WITH MODERATE HYPERHOMOCYSTEINEMIA

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Abstract: Increased concentration of homocysteine is a risk factor for stroke, peripheral vascular disease, myocardial infarction, and venous thromboembolism. It seems that hyperhomocysteinemia affects not only the blood coagulation system, but also the vascular wall structure. MTHFR gene encodes a co-substrate for homocysteine remethylation to methionine, but it is also involved in transsulfuration to cystathionine. We present the case of a 42-year-old man hospitalized for treatment and functional rehabilitation in Medical Rehabilitation Clinical Hospital Băile Felix, Romania, after ischemic stroke. The patient with unremarkable anamnesis, negative family history, no known diagnosis of homocystinuria developed an acute cerebrovascular ischemic accident. MRI described an ischemic vascular lesion of the left cerebellar hemisphere with edema, herniation phenomena through foramen magnum and supratentorial and amputation of the fourth ventricle. Ultrasonography of the heart and precerebral arteries revealed normal aspects. The most significant laboratory finding was moderate hyperhomocysteinemia. Molecular analysis revealed the presence of a heterozygous MTHFR C677T mutation and the absence of A1298C mutation. After drug therapy, he was admitted in our clinic at about one month after the vascular accident, having only coordination problems. Rehabilitation treatment was complex and involved coordination of several team members, with the following main objectives: coordination and balance in physical activities, through stimulation exercises specific for occupational therapy and kinetherapy. He showed significant improvement after three weeks of intensive treatment. Prompt response to the rehabilitation programme in this case is another argument for early, individualized treatment, which continues at home, over a long period of time.

Cuvinte cheie:
hiperhomocisteinemie,
accident vascular
cerebral, reabilitare

Rezumat: Concentrația crescută de homocisteină este un factor de risc pentru accident vascular cerebral, boală vasculară periferică, infarct miocardic și tromboembolism venos. Se pare că hiperhomocistinemia afectează nu numai sistemul de coagulare al sângelui, ci și structura peretelui vascular. Gena MTHFR codifică un co-substrat pentru reacția de remetilare a homocisteinei la metionină, dar este, de asemenea, implicată și în transsulfurarea la cistationină. Prezentăm cazul unui bărbat de 42 de ani, internat pentru tratament și reabilitare funcțională la Spitalul Clinic de Recuperare Medicală Băile Felix, România, după accident vascular cerebral ischemic. Pacientul cu anamneza nesemnificativă, istoric familial negativ, fără diagnostic cunoscut de homocistinurie a dezvoltat un accident vascular cerebral ischemic acut. Examinarea RMN a descris o leziune vasculară ischemică din emisfera cerebeloasă stângă cu edem, fenomene de herniere prin foramen magnum și supratentorial și amputarea ventriculului IV. Ecografia cardiacă și a arterelor precerebrale au relevat aspecte normale. Constatarea cea mai importantă de laborator a fost hiperhomocistinemie moderată. Analiza moleculară a relevat prezența unei mutații MTHFR C677T în heterozigoție și absența mutației A1298C. După terapia medicamentoasă, a fost internat în clinica noastră, la aproximativ o lună după accidentul vascular, având probleme de coordonare. Tratamentul de recuperare a fost complex și a implicat coordonarea mai multor membri ai echipei, cu următoarele obiective principale: coordonare și echilibru în activitățile fizice, prin exerciții de stimulare specifice terapiei ocupaționale și kinetoterapiei. El a prezentat o îmbunătățire funcțională semnificativă, după trei săptămâni de tratament intensiv de recuperare. Răspunsul prompt la programul de reabilitare în acest caz este un alt argument pentru tratament individualizat, precoce, care continuă la domiciliu pe o perioadă lungă de timp.

INTRODUCTION

Homocystinuria comprises a group of hereditary diseases characterized by elevated levels of homocysteine in urine. These metabolic disorders are caused by an enzymatic deficiency. Different types of mutations lead to the lack of enzymes involved in degradation or reformation of methionine.

Three primary homocystinuria types were described:(1)

1. Classic homocystinuria (due to cystathionine β - synthasedeficiency),
2. Methylene tetrahydrofolate reductase (MTHFR) deficiency,
3. Homocystinuria due to cobalamin (vitamin B12) metabolic defects.

Of these forms, homocystinuria due to MTHFR deficiency (OMIM ID: 236250) is considered to be a rare

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condition that leads to elevated homocysteine levels in plasma and urine.(2) Clinical features for the severe form include microcephaly, developmental delay, lack of coordination or epilepsy.(3,4) Blood vessel disease may also occur causing stroke or seizures.(5)

Enzyme deficiency is caused by mutations in MTHFR gene and is inherited as an autosomal recessive trait.(6)

Treatments in MTHFR deficiency may use folic acid, vitamin B6 and vitamin B12. In contrast to classic homocystinuria, in MTHFR deficiency, the methionine level is low and methionine supplementation has also been tried.(1)

An increased level of homocysteine is considered to be a risk factor for stroke.(7,8) It is not yet known if lowering homocysteine level might reduce the risk for stroke. Saposnik et al. aimed to determine whether vitamin therapy reduced the risk of ischemic and hemorrhagic stroke, as well as stroke-related disability. Mean homocysteine concentration decreased in the vitamin therapy group and increased in the placebo group. The incidence rate of stroke was 0.88 per 100 person-years in the vitamin therapy group and 1.15 per 100 person-years in the placebo group.(9) They concluded that lowering of homocysteine level with folic acid, vitamin B6 and vitamin B12 did reduce the risk of overall stroke, but did not reduce severity of stroke and disability after stroke.

Rehabilitation after stroke has to begin as soon as possible. Multiple therapies are used over the course of recovery. There are two main objectives: combating immobilization syndrome and promoting motor recovery.

CASE REPORT

We present the case of a 42-year-old man hospitalized for treatment and functional rehabilitation in Medical Rehabilitation Clinical Hospital Băile Felix, Romania, after ischemic stroke. The patient with unremarkable anamnesis, negative family history, no known diagnosis of homocystinuria developed an acute cerebrovascular ischemic accident.

The patient with no known medical history, presented dizziness, balance problems with failure to maintain orthostatism, nausea, vomiting, occipital headache, diplopia, symptoms with sudden onset that persisted until admission, with moderate worsening. Brain MRI revealed ischemic cerebral vascular lesion of the left cerebellar hemisphere with edema and herniation through foramen magnum and supratentorial, amputation of the fourth ventricle. He was hospitalized in the Neurology Clinic for further investigation and therapy.

Brain MRI performed 2 days later, revealed extensive stroke located in the lower 1/2 of left cerebellar hemisphere, including the left cerebellar tonsil, size 62/58/54 mm, with compressive effect on the fourth ventricle and on bulbopontine adjacent structures. Suprajacent active triventricular hydrocephaly, with paraventricular exudation. Flattening of peripontine cisterns. Magnetic resonance angiography revealed normal data.

During hospitalization, he followed neurotropic treatment, antiaggregant treatment, statins and antivertigo therapy, with favourable evolution.

After 6 days of intensive specific drug treatment, brain MRI investigation was repeated and an important reduction of cytotoxic edema in the left cerebellar ischemic area as well as disappearance of compression effect on the fourth ventricle were found.

Ultrasonography of the heart and precerebral arteries revealed normal aspects.

The most significant laboratory finding was moderate hyperhomocysteinemia, homocysteine value was 13.46 micromol/l.

Interpretation:

<10 micromol/l	ideal
10-12 micromol/l	acceptabil for healthy subjects
>12-30 micromol/l	moderate hyperhomocysteinemia
>30-100 micromol/l	intermediate

hyperhomocysteinemia

>100 micromol/l severe hyperhomocysteinemia
Molecular analysis revealed the presence of a heterozygous MTHFR C677T mutation. Molecular investigation also revealed:

- absence of factor V mutations
- absence of MTHFR A1298C mutation

Conclusion: genetic risk of thrombosis.

The evolution was favourable and he was discharged with the following recommendations:

- neurological dispensarization
- medication
- medical rehabilitation

Drug therapy was the first therapeutic step, then he was admitted in our clinic for functional rehabilitation, at about one month after the vascular accident, having coordination problems. Rehabilitation treatment was complex and involved coordination of several team members, with the following main objectives: coordination and balance in physical activities, through stimulation exercises specific for occupational therapy and kinetotherapy.

Principles of coordination represented the basis, when establishing an exercise.

Working for coordination will be done as follows:

- Exercises will be performed several times a day without interruption, until coordination is achieved.
- Any unnecessary contraction should be avoided - excitation radiation should not occur, as it can compromise coordination.
- Strengthening accurate sensory perception through verbal explanations, cinematic records, drawings.
- Patient focusing - any sign of fatigue interrupts training.
- It is not performed with great force - the lower is the resistance, the lower the excitation radiation in the CNS and coordination increases, sometimes work is done with less than 10 % of the maximum force.
- In any coordination programme, exercise will be performed faster and faster, the speed is the proof of accuracy.

Occupational therapy aimed improving activities of daily living:

1. Self-care activities:

- Shaving in the mirror - which means viewing the movement in the mirror and moving the hand in the same time.
- Washing in orthostatic position in front of a mirror,
- Preparing meals in orthostatic position.

2. Household activities:

- Arranging books on the top shelf in the library,
- Arranging clothes in the closet.

3. Gainful activities:

- to fix an object at a certain height on the wall,
- painting a room from a ladder.

Methods used to achieve the objectives are:

1. Exercises that stimulate balance and coordination in the laboratory of Occupational Therapy:

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- Exercises on Bobath ball of different sizes, where the patient must maintain balance sitting on this
- Various exercises performed on unstable surfaces: walking on a mattress while having other two objects in his hands and at the same time numbering every three counts downward from 57 to 4. Here, we wanted to give more tasks in order to obtain a better performance.
- Exercises on rocking chair in front of the mirror while hitting two balls
- Exercises in "Balance Trainer" with Biofeedback, equipment located in the Occupational Therapy cabinet.

§ E.g.: Over obstacles of different sizes with the sudden change of direction

§ E.g.: With the eyes closed, to stimulate proprioception, the patient being on an unstable surface

2. Rapid climbing and particularly descending stairs,
3. Walking on ice,
4. Walking on uneven ground,

Recommendations:

- mountain hiking
- skiing
- skating
- walking on the sand, through the waves, at different speeds with the sudden change of direction
- cycling .

Recommended sports:

- Tennis for hand - eye - foot coordination
- Handball
- Basketball, or any other sport pleasant for the patient, which would stimulate coordination and balance in walking and standing.

The patient showed significant improvement after three weeks of intensive treatment.

DISCUSSIONS

Stroke is an important cause of death and disability. It is estimated that 80% of strokes are ischaemic. Several single-gene diseases are important causes of stroke, especially in young individuals, in some of these stroke may be the prevailing manifestation and in others is part of a larger spectrum of manifestations.(10) Increased concentration of homocysteine is a risk factor for stroke, peripheral vascular disease, myocardial infarction, and venous thromboembolism.(11,12,13) It seems that hyperhomocysteinemia affects not only the blood coagulation system, but also the vascular wall structure.(14,15) MTHFR gene encodes a co-substrate for homocysteine remethylation to methionine, but it is also involved in transsulfuration to cystathionine.

Factor V Leiden, factor II G20210A mutation and polymorphism of methylenetetrahydrofolate reductase gene (MTHFR) are considered important hereditary risk factors for thromboembolic events.(16,17)

Determination of homocysteine levels is useful especially in patients with stroke at young ages, with negative history for vascular disease or thrombosis or with positive family history for premature atherosclerosis.(18) Rehabilitation after stroke must be initiated early in order to be effective. Thus, medical interventions enhance the recovery process and minimize functional disability.(19)

Our patient had coordination problems. Coordination means the combination of a number of muscle activity in a continuous, smooth motion scheme, made under normal conditions and needs control. It is automatic, not made consciously, though it may also be made consciously.

Coordination cannot be recovered until stability strength and mobility were achieved. Coordination requires many repetitions. It requires training to increase the accuracy with maximum economy of muscular effort. Only thus, any unnecessary radiation of excitation and any parasitic motion are inhibited.

CONCLUSIONS

Mutation detection is helpful in establishing etiology, the risk of thrombosis and in providing genetic counselling.

Prompt response to the rehabilitation programme in this case is another argument for early, individualized treatment, which continues at home, over a long period of time.

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