Homocystinuria: Diagnosis and Neuroimaging Findings of Iranian Pediatric Patients

How to Cite This Article: Karimzadeh P, Jafari N, Alai MR, Jabbehdari S, Abadi FA, NejadBiglari H. Homocystinuria: Diagnosis and Neuroimaging Findings of Iranian Pediatric Patients. Iran J Child Neurol. 2015 Winter;9(1):94-98.

Abstract
Objective
Homocystinuria is a neurometabolic diseases characterized by symptoms include Neurodevelopmental delay, lens dislocation, long limbs and thrombosis.

Materials & Methods
The patients who were diagnosed as homocystinuria marfaniod habits, seizure in the Neurology Department of Mofid Children's Hospital in Tehran, Iran between 2004 and 2014 were included in our study. The disorder was confirmed by clinical and neuroimaging findings along with neurometabolic and genetic assessment from reference laboratory in Germany. We assessed age, gender, past medical history, developmental status, clinical manifestations, and neuroimaging findings of 20 patients with homocystinuria.

Results
A total of 75% of patients were offspring from consanguineous marriages. A total of 95% of patients had a history of developmental delay and 40% had developmental regression. A total of 75% had seizures from these 45% showed refractory seizures. Seizures among 13 patients were controlled with suitable homocystinuria treatment. The patients with homocystinuria were followed for approximately 10 years and the follow-ups showed that the patients with an early diagnosis and treatment had more favorable clinical responses for growth index, controlled refractory seizures, neurodevelopmental status, and neuroimaging findings. Neuroimaging findings include brain atrophy and/or white matter involvement.

Conclusion
According to the results of this study, we suggest that early assessment and detection play an important role in the prevention of disease progression and clinical signs. Homocystinuria in patients with a positive family history, developmental delays, or regression, refractory, or recurrent seizures should take precedence over other causes.

Keywords: Homocystinuria; Neurometabolic disorder; Early detection

Introduction
Homocystine is an amino acid with sulfur that comes from methionine metabolism. Homocystine is metabolized by two pathways as follows: transsulfuration or remethylation (1). Gene abnormalities in the enzymes, which catalyze the reactions in trans sulfuration or remethylation pathways, can cause...
hyper homocysteinuria. Homocystinuria can be caused by abnormal DNA methylation during embryogenesis(2). Hyperhomocystinuria is caused by a rare genetic error caused by deficiencies in methylenetetrahydrofolate reductase, cystathionine beta synthase, or in enzymes involved in homocystine methylation and methyl-B12 synthesis(3). There is an association between mutations of elevated levels of homocysteine, methylenetetrahydrofolate reductase, MTHFR C677T, and increased risk of thrombosis among homozygous carriers. Heterozygote carriers for the above gene mutations with other major or minor risk factors are prone to thrombosis (4). Mutation of the methylenetetrahydrofolate reductase (MTHFR) and provides the folate derivative for homocystine to methionine conversion. This mutation can cause mild hyperhomocysteinuria. The rationale (folate supplementation) can be used to overcome the genetic deficiency in cases with low levels of folate(5). High levels of homocystine in plasma are one of the risk factors for atherosclerosis (6). It has been showed that early detection and treatment can be helpful and homocystine levels can be controlled by vitamins B6, B12, cofactors needed for homocystine metabolism, and by folic acid supplements (7-9).

In this study, we present 10 years of experience about homocystinuria from the Pediatric Neurology Research Center of Mofid Children’s Hospital, Tehran, Iran. We describe clinical symptoms and neuroimaging findings for 20 cases with this disorder.

Materials & Methods
This observational study was performed on patients who were diagnosed with homocystinuria at the Neurology Department of Mofid Children’s Hospital in Tehran, Iran, from 2004–2014. The diagnosis was performed based on clinical manifestations, neuroimaging findings, homocystine level assessments in Germany, and, finally, genetic study. The data collected were age, gender, past medical history, developmental status, general appearance, and clinical and neuroimaging findings.

Treatment consisted of betaine, carnitine, folic acid, vitamin B12, vitamin B6 supplements, a low-protein diet, and anti-convulsant drugs in cases with seizures.

The children’s diet was carefully controlled. The data were analyzed by descriptive methods and no statistical testing was applied.

Institutional ethical approval for the conduct of this study was obtained from the Pediatric Neurology Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran. All parents signed a written consent for participation in the study.

Results
Twenty patients with homocystinuria who had been assessed and followed over the last 10 years were included in this study. Six patients, in addition to homocystinuria, had methylmalonicacidemia. There were 11 males and 9 females with an age range from 6-months to 15-years. The earliest case was diagnosed in a neonate who presented with a sepsis-like illness and the latest case was diagnosed in a 10 year-old with seizures due to cerebral thrombosis after lens dislocation surgery. The average age of patients at final detection time was 9.6 months. A total of 75% of patients were offspring from consanguineous marriages. In addition, 5 patients had a positive family history of similar disease and 2 of them died without diagnosis.

One of our patients (39 months old) died about 2 years after detection. The patient had not received any treatment due to his parent’s decision.

Four patients had a history of neonatal hospitalization because of poor feeding in patient-number 1, was diagnosed at that time, and treatment of homocystinuria was started. Patient-number 2 had continuous vomiting that was permanent until 4 months of age and homocystinuria was detected at this time. Patient-number 3 had sepsis-like illness from 12 days of age but was diagnosed at 9 months of age. Patient-number 4 had a neonatal hospitalization due to hyper bilirubinemia. The chief complaints in patients at detection time were seizures in 11 patients and developmental delays or regression in 7. Two cases had visual loss. In the developmental assessment, 19 patients had developmental delay, 8 patients had developmental regressions with words and movements stuck more than their recognition. Fifteen patients had seizures of which 9 patients had recurrent and refractory. The types of seizures were as follows: 5 patients had generalized
Homocystinuria: Diagnosis and Neuroimaging Findings

Homocystinuria is a rare inborn error of the metabolism with autosomal recessive inheritance that is caused by enzyme deficiencies (3). Homocystinuria is caused by genetic mutations in the enzymes and may contribute to increases in plasma homocystine. First, Carson and Neill reported the association between mental retardation and homocystinuria in two Irish brothers in 1962 (10). In 1964, Gerritsen and Waisman first identified homocystine in the urine and defined homocystinuria (11). Prior to the 1960s, in 1933, homocystinuria had already been described in an eight-year-old child with mental retardation, dislocation of the lens, and skeletal abnormalities with coxavara and who died from a stroke (12). Homocystinuria was diagnosed in this child’s nephew in 1965 (13). Normal levels of plasma homocysteine are between 5–15 nmol/ml and concentrations between 16–30 nmol/ml is mild, 31–100 nmol/ml is moderate, and greater than 100 nmol/ml is severe hyperhomocystinuria (14). Mudd SHet al reported that around half of their cases had a good laboratory and clinical response to high doses of vitamin B6 (15). Fonseca et al had no known relevant clinical findings in family members (16). Treatment for elevated homocystine levels is simple and innocuous. High doses of pyridoxine (B6) were used initially with success in children with homocystinuria (17).

The clinical features include subluxation of the lens, which are characteristic for connective tissue disorders (15). Our results were similar and five patients had visual loss from lens dislocation and secondary cataracts. Twenty patients (11 males and 9 females) with homocystinuria were included in this study. A total of 75% of cases were from consanguineous parents and 25% had similar diseases in their families. Therefore, in suspected cases of homocysteinuria, having consanguineous parents can contribute to the diagnosis because of autosomal recessive inheritance of homocysteinuria. A total of 15% of patients had a history of hospitalization due to period of sepsis-like illness that metabolic disease assessment can be helpful in detection for ill neonates. A total of 95% of patients had a history of developmental delay and 40% had developmental regression. Patients with these symptoms who are referred to a pediatric neurologist,
it is our suggestion to for the pediatric neurologist to consider homocysteinuria. A total of 35% of patients had heights greater than normal and 40% of patients had skin and hair involvement, i.e. skin lesions and blond hair, among others.

From brain MRIs, 75% of patients had brain involvement (generalized atrophy, white matter involvement, previous infarct pattern, and venous sinus thrombosis). In follow-up imaging, which was done in 6 patients, 50% of them had improvements in white matter involvement and brain atrophy. Sachdeva Vet al reported that all patients had ischemic lesions in the brain MRI with contrast (18).

A total of 75% of patients had seizures and 45% of these seizures were current and refractory. Seizures were controlled for 13 patients after starting anti-epileptic drugs and special treatment for homocysteinuria. Regression in our patients was stopped after starting treatment and 62% of patients regained that ability. In addition, further strokes after treatment did not occur.

Our patients with homocystinuria came to our specialist center and exact evaluations were done.

In conclusion, based on our results, patients with developmental delay or regression, long limbs and tall, recurrent seizures, skin lesions, blond hair, eye involvement such as secondary cataracts due to lens dislocation, hypotonia, brain involvement in MRI include brain atrophy or white matter involvement, and having a positive family history of homocystinuria then homocystinuria disorder should be considered.

Acknowledgments
We thank Wagnester laboratory in Germany for conducting laboratory tests for neurometabolic disorders. In addition, we thank the parents of our patients for their cooperation and permission to publish this study. Declaration of conflicting interests: None declared.

Funding: The authors received no financial support for the research and publication of this article.

Author contribution
Dr. Karimzadeh was responsible for the study design, collection, and interpretation of clinical data and oversaw all stages of revision and editing.

Dr. Jafari contributed in the collection of data and wrote the first draft of this manuscript. Other coauthors were involved in the data collection and interpretation. All authors reviewed the draft of this article and agreed to submit this final version of the manuscript.

References
1. Brustolin S1, Giugliani R, Félix TM. Genetics of homocystine metabolism and associated disorders. Braz J Med Biol Res 2010 Jan; 43(1):1-7.
2. Iacobazzi V, Infantino V, Castegna A, Andria G.
3. Selhub J. Homocystinuria: Related genetic diseases and congenital defects, abnormal DNA methylation and newborn screening issues. Mol Genet Metab 2014 September - October; 113(1-2):27-33.

Fig 1. A-15-year–old male with brain involvement due to Homocystinuria
1999;19:217-46.

4. Ali Z, Troncoso JC, Fowler DR. Recurrent cerebral venous thrombosis associated with heterozygote methylenetetrahydrofolate reductase C677T mutation and sickle cell trait without Homocysteinuria: An autopsy case report and review of literature. Forensic Sci Int 2014 Sep;242:e52-5.

5. Rozen R. Genetic modulation of Homocysteinuria. Semin Thromb Hemost 2000;26(3):255-61.

6. Palma Reis R, Sales Luis. Homocisteinemia e Doença Vascular – O Nascer de um Novo Factor de Risco. Rev Port Cardiol 1999; 18:507-14.

7. McCully KS. Homocystine theory of arteriosclerosis: development and current status. Atherosclerosis Rev 1983;11:157-246.

8. Malinow MR. Homocystinuria: a common and easily reversible risk factor for occlusive atherosclerosis. Circulation 1990;81:2004-6.

9. Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocystine as a factor for vascular disease: probable benefits of increasing folic acid intakes. JAMA 1995;472:1049-57.

10. Carson NAJ, Neill DW. Metabolic abnormalities detected in a survey of mentally backward individuals in Northern Ireland. Arch Dis Child 1962;37:505-13.

11. Gerritsen T, Waisman HA. Homocystinuria, an error in the metabolism of methionine. Pediatrics 1964;33:413-20.

12. Mallory T. Case records of the Massachusetts General Hospital. Case 19471. Marked cerebral symptoms following limp of three months duration. N Engl J Med 1933;209:1063-6.

13. Shih VE, Efron ML. Pyridoxine-unresponsive homocystinuria. Final diagnosis of MGH case 19471. N Engl J Med 1970;283:1206-8.

14. Kang SS, Wong PWK, Malinow MR. Hyperhomocyst(e)emia as a risk factor for occlusive vascular disease. Ann Rev Nutr 1992;12:279-98.

15. Mudd SH, Skovby F, Levey HL, et al. The natural history of homocystinuria due to cystathionine B-synthase deficiency. Am J Hum Genet 1985;37:1-31.

16. Fonseca N1, Vidal N, Santos J, Brito AP, Bernardino L, Silvestre I, Inês L. Hyperhomocysteinuria—case report. Rev