# Iranian Journal of Neurology

*Official Journal of Iranian Neurological Association*





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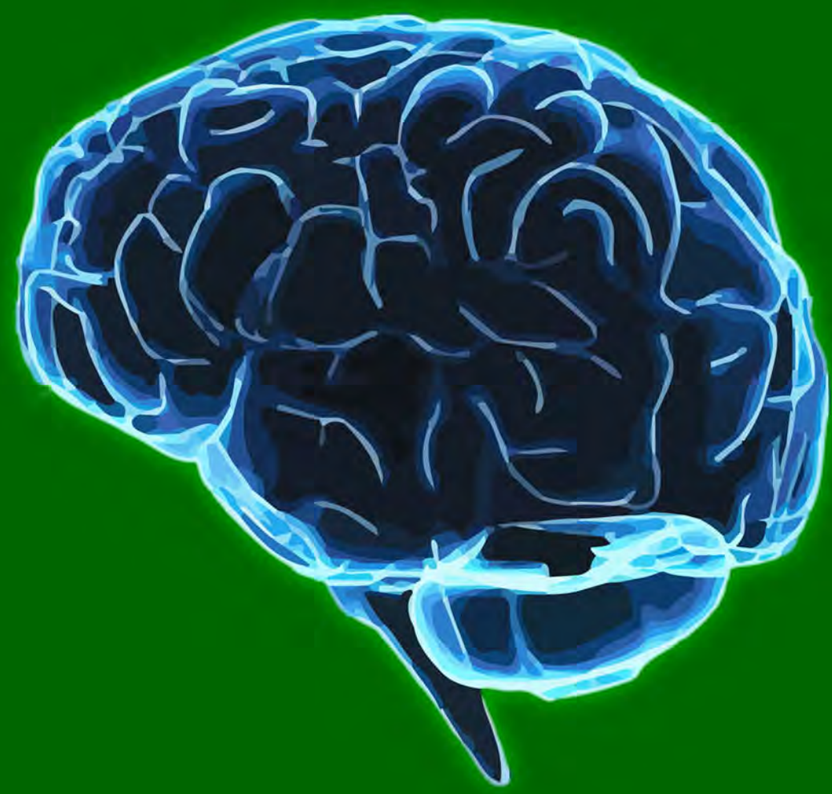
*Iranian Journal of Neurology*

Volume 14, Issue 1, Winter 2015


Volume 14, Issue 1, Winter 2015
ISSN: 2008-384X
*ijnl.tums.ac.ir*

# Iranian Journal of Neurology

**Volume 14, Issue 1, Winter 2015**





**Email: ijnl@tums.ac.ir** **http://ijnl.tums.ac.ir**

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Iranian Journal of Neurology

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- Page 3 and subsequent pages: manuscript body including Introduction, Materials and Methods, Results, Discussion, Conclusion, References, Tables, Figures

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In any time the evidence of plagiarism is detected, the manuscript will be withdrawn and the author will be sanctioned from publishing papers permanently.

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# *Table of Contents*

Iranian Journal of Neurology

Review Article

Iran J Neurol 2015; 14(1): 1-7

# Epileptic syndromes: From clinic to genetic

Received: 10 Jan 2014
Accepted: 15 Sep 2014

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**Keywords**
Epilepsy, Genetic, Inheritance, Chromosomal Abnormalities, Mutation

**Abstract**
Epilepsy is one of the most common neurological disorders. Studies have demonstrated that genetic factors have a strong role in etiology of epilepsy. Mutations in genes encoding ion channels, neurotransmitters and other proteins involved in the neuronal biology have been recognized in different types of this disease. Moreover, some chromosomal aberration including ring chromosomes will result in epilepsy. In this review, we intend to highlight the role of molecular genetic in etiology of epilepsy syndromes, inspect the most recent classification of International League against Epilepsy and discuss the role of genetic counseling and genetic testing in management of epilepsy syndromes. Furthermore, we emphasize on collaboration of neurologists and geneticists to improve diagnosis and management.

## Introduction

### *Epilepsy*

*Definition*

"Epilepsy" is derived from the Latin term meaning, "to be attacked." In medicine, epilepsy is defined as recurring episodes of seizures due to excessive and abnormal synchronous neural activity of the cerebral cortex, which could be induced by cellular or molecular defects in cerebral tissues.[1] In cases of an altered endocrine or metabolic state, it would be categorized as structural/metabolic epilepsy. However, on occasions the underlying disorder could not be recognized, and it would be classified under unknown category. Epilepsies attributed to known genetic disorders are classified as genetic epilepsies[2] (refer to the next section).

Annual incidence of seizures in the general population is estimated to be 61/100,000 persons[3] with higher occurrence in both extremes of life.[4]

Clinical diagnosis of epilepsy is carried out mainly by evaluation of patient's detailed history. Positive electroencephalogram (EEG) results are supportive for confirmation of epilepsy. Nevertheless, negative findings might not exclude the diagnosis of epilepsy.[5,6] Clinical presentation of epilepsy may easily be mistaken with conditions mimicking seizure's features, including hypoglycemia, sleep disorders, migraines, transient ischemic attacks and transient global amnesia.[7,8]

*Classification*

Based on the 2010 report of International League Against Epilepsy (ILAE),[9] the etiology of epileptic seizures is divided into three major classes as discussed below.

Genetic epilepsy: this category (previously known as idiopathic) implies epileptic disorders that are a direct consequence of either known single gene defects or complex inheritances in which the epilepsy is the essential symptom. Nonetheless, the



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contribution of environmental factors in disease expression cannot be disregarded.[2,9] The recent alternation of "idiopathic" to "Genetic" has the advantage of highlighting the genetic predisposition, and it no longer conflate other concepts (e.g. prognosis). Most cases display clinical features during childhood or adolescence. Although some suffers from a variety of subtle cognitive and behavioral challenges, the affected patients may have normal intelligence, and EEG might also show generalized discharges.[9,10] Genetic epilepsy is further divided into generalized and partial epilepsy. Childhood absence epilepsy, juvenile myoclonic epilepsy and epilepsy with grand-mal seizures on awakening are examples of genetic generalized and benign focal epilepsy of children is an instance of partial genetic epilepsy.[2,9]

Structural/metabolic epilepsy: Epilepsies classified under this category (previously known as symptomatic) require specific structural or metabolic defects that have been demonstrated to be associated with considerably higher risk of epilepsy. Genetic abnormalities, including mutations and chromosomal abnormalities (e.g. tuberous sclerosis) might be the origin of this category of epilepsy with a particular metabolic or structural disorder inserted between genetic defect and occurrence of epilepsy.[9]

Unknown epilepsy: this category has replaced the previous classification known as cryptogenic. It should be noted that this category contains epileptic disorders, which the underlying cause is not yet determined and could be a consequence of a genetic or separate defect.[9,11] Considering the enhancement of genetic methods and improved neuroimaging techniques, the prevalence of unknown epilepsy is decreasing.[11]

***Role of genetic in etiology of epilepsy***

Since establishment of Mendelian Inheritance laws in 1865, modern science launched numerous investigations to discover the role of genetics in pathology of human diseases. The recognized scholarly debate of nature versus nurture, a popular concept in epilepsy disorders, have influenced research agendas for a century and many pioneers tried to unveil this mystery by studying monozygote (MZ) vs. dizygote twins (DZ).[12-15] These approaches provide an opportunity to decompose the variables into genetic and environmental factors. Identical twins share about 100% of their genes, while fraternal twins share nearly 50%, and both share many aspects of the environment by virtue of being born in the same place and time. Detection of a particular trait to be substantially more common in MZ twins implicates the importance and strength of genetic determinants in expression of the specific trait.[16]

Concordance of epilepsy has been estimated 62% in MZ pairs compared with 18% in DZ twins.[13] Large twin population studies suggest a higher rate of epilepsy syndromes in MZ pairs,[13-15] specifically generalized epilepsy.[13] These findings propose the involvement of syndrome-specific genetic determinants in pathology of this group of disorders.

It has been estimated that genetic epilepsy affects 0.3-0.5% of general population.[1,17] Children of one parent with genetic epilepsy have a 4-6% risk, while children of both parents with genetic epilepsy have a 12-20% risk.[1]

Recent reports have highlighted the importance of genetic predisposition in epilepsy syndromes, as ILAE has altered the previous "idiopathic" category to "genetic" and has approved of genetic testing for patients and families affected by epileptic syndromes including X-linked infantile spasm, Dravet syndrome, Ohtahara syndrome, and early-onset absence epilepsy.[18] Furthermore, the new approaches to sequence DNA is revealing specific gene defects and linking them to distinct clinical features of genetic epilepsies.[8]

Genetic epilepsies could further divide into four subgroups according to the mechanism of inheritance: (1) genetic epilepsy with Mendelian inheritance, (2) epilepsies with complex inheritance, (3) genetic epilepsies associated with cytogenetic abnormalities and (4) Mendelian disorders in which epilepsy is one of the manifestations. The former class is thought to account for a small number of epilepsies, and the disease occurrence could be tracked through generation. A proper pedigree analysis will affirm whether the phenotype is dominant or recessive, autosomal or X-linked (Figure 1).[11] Epilepsies with complex inheritance are believed to be involved in 50% of epilepsies.[11,19] Although familial aggregation is seen through generations, the mode of inheritance cannot easily be identified.

Detection of a specific chromosomal abnormality (either structural or numerical) would be categorized under genetic epilepsies with cytogenetic abnormalities.[11] This subgroup is mostly associated with other neurological disorders and facial anomalies.

Mendelian disorders in which epilepsy is one of the manifestations indicate multisystem disorders with epilepsy as one of the characteristics. These syndromes include neurocutaneous and neurodegenerative disorders and a cluster of metabolic diseases.[11] Thus, the genetic counselor might be able to asses these syndromes. However, such disorders could hardly be considered an epileptic disease since epilepsy occurs as a secondary symptom.

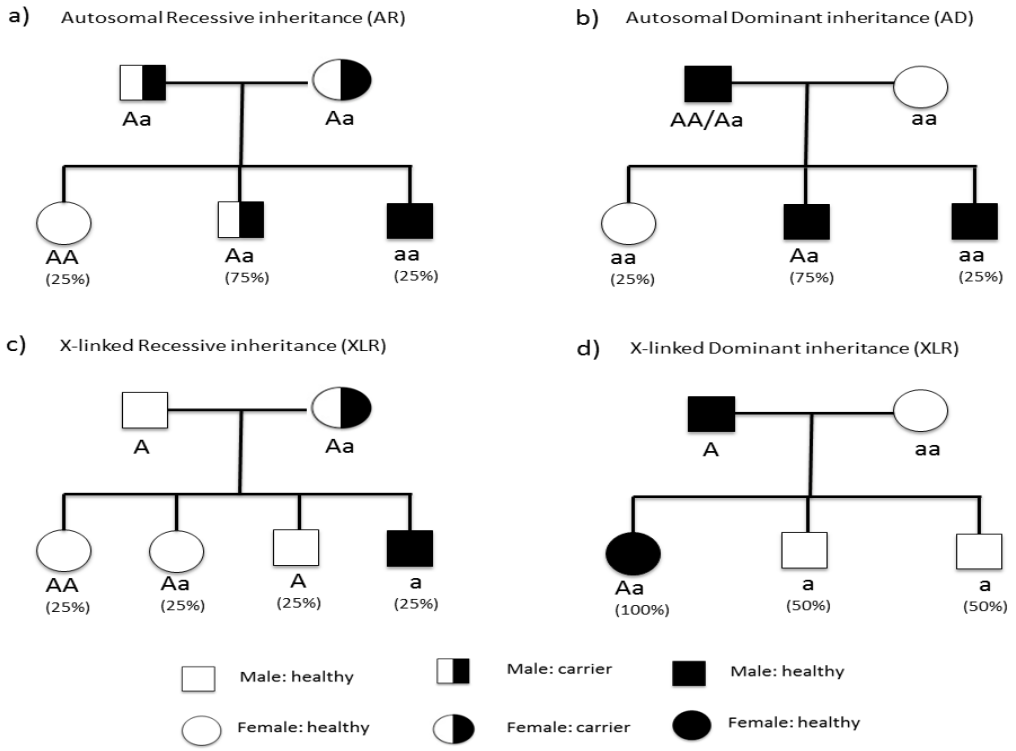


**Figure 1.** Mendelian modes of Inheritance (a) autosomal recessive inheritance. In this case "a" is the mutated allele of the gene and "A" is non-mutated. Individual who receives mutated allele from both parents (aa) would be affected with disease. Another persons "AA" and "Aa" do not show phenotypes of disease. (b) Autosomal dominant inheritance. In this model "A" (the dominant allele) is mutated allele and can cause disease, so any individual who receives just one mutated allele (AA, Aa) would be affected. (c) X-linked recessive inheritance. This mode has sex-based transmission because the gene is located on X chromosome, therefore females have two alleles of the gene and males have just one allele. If the mother is carrier, 50% of her boys will be affected and none of the girls in such pedigrees would show the phenotype of disease. (d) X-linked Dominant inheritance. In this example, the disease is caused by dominant mutated allele located in chromosome X. So if the father is affected, all the girls would be affected and no boys would show the disease phenotype. If the mother was affected too (Aa or AA) so the boys would have shown the phenotype of disease with different percentage

The following section is dedicated to reviewing the role of chromosomal abnormalities and gene mutations in etiology of epileptic syndromes with some examples. We are referring interested readers for a complete list of genes mutated in epilepsies to two reviews written by Garofalo et al.[20] and Kaneko et al.[21]

*Chromosomal aberrations*

Chromosomal aberration is characterized by atypical number or structural abnormality of at least one chromosome that usually leads to genetic disorders. In numerical group, aneuploidy is usually due to abnormal gametogenesis in parents.[22] Considering aneuploidy is accompanied with gaining or losing considerable amount of genetic materials, apart from sex chromosome disorders it is a fatal.[23] However, there are few cases of live birth. These patients usually suffer from facial dysmorphisms and mental retardation as well as seizure.[24,25] Conventional karyotyping could easily identify numerical chromosomal aberrations.[26]

There are several forms of structural chromosomal abnormalities including deletion, duplication and translocation of portion of a chromosome. These defects are not generally fatal, and newborns with structural abnormalities may have developmental delay and facial dysmorphism.[27] Epilepsy is one of the widespread features in this group of anomalies.

Ring chromosomes detection might help discovering genetic epilepsy.[28-30] A ring chromosome is usually formed through breakage of both ends of the chromosome and fusion of arms. Back et al. have reported a phenotypically normal woman with ring chromosome 20 who had two children suffering from mental retardation, behavioral disorder, and epilepsy.[31] In addition, EEG of epileptic patients with

ring chromosome 20 has a distinct feature of prolonged high-voltage slow waves and seizures are resistant to medications.[28] Ring chromosome 14 has also been reported to be resistant to antiepileptic therapy.[32] The onset of epilepsy in this chromosomal disorder is often during the first year, mental retardation would be a constant character and the majority of cases have dysmorphic facial features. EEG frequently reveals focal abnormality.[32]

Chromosome 6q deletion (Long arm of chromosome 6) and chromosome 22q duplication have been shown to be associated with dysmorphic facial abnormalities, mental retardation and epilepsy.[33,34]

As a result of high-resolution karyotyping, many epileptic seizures have been linked to chromosomal abnormalities.[35-37] Aberrations such as microdeletions and microduplications (microchromosomal defects) that could not be detected by conventional karyology might be identified by molecular cytogenetic approaches including comparative genomic hybridization (CGH) array and multiplex ligation-dependent probe amplification (MLPA).[38-41] Exploring the nature of the human genome with high repetitive DNA sequences lead to discovering recurrent rearrangements of regions in some chromosomes such as 15q and 16p that are involved in epilepsy could result in recurrent heritable microdeletions and microduplications.[42]

***Gene mutations***

In addition to chromosomal abnormalities, gene mutations also could be associated with epilepsy syndromes. A good example would be genes encoding ion channel subunits.[43,44] Excitatory or inhibitory neurotransmitters in central nervous system[45] have also been recognized in Mendelian forms of epilepsy[11,46,47] and thus, following simple Mendelian mode of inheritance.[46,47] Genetic counseling could help identifying these disorders through a prodigy and risk of disease could be estimated for the next generation.

CHRNA4 gene encodes neural acetylcholine receptor subunit α4.[48] It was the first gene to be associated with epilepsy syndromes. Mutation in this gene has been linked to Autosomal dominant nocturnal frontal lobe epilepsy.[49,50] KCNQ2 and KCNQ3 genes that encode voltage-gated potassium channels were identified in families affected with benign familial neonatal seizures.[51,52]

At least 37 genes for generalized myoclonic epilepsy and febrile seizures, 47 genes for symptomatic (structural/metabolic) epilepsy and 30 genes for epileptic encephalopathies have been recognized.[20] In a recent study of pediatric patients affected with infantile spasms and Lennox-Gastaut syndrome, two forms of epileptic encephalopathies, and their parents, researchers found 329 de novo mutations.[53] These mutations are significantly more prominent in genes sets regulated by fragile X protein. Mutation of fragile X protein has been extensively discussed in autism spectrum disorders as it is the most widespread single-gene cause of autism [54]. Further genetic defects involved in epileptic encephalopathies include MTOR, GABRA1 and FLNA.[53]

Mutation in SCN1A, a gene encoding voltage-gated sodium channel, has been demonstrated to be involved in Dravet syndrome. The affected patients suffer from severe myoclonic epilepsy during infancy with poor prognosis, as seizures are frequent, prolonged and resistant to treatment. Developmental delay will appear and some would have cognitive impairment. There are reports of mutation in PCDH19, a gene that encodes a calcium-dependent cell-adhesion protein and is located on chromosome X, in female patients with clinical symptoms related to Dravet syndrome.[55,56] Interestingly, 11-12% of affected patients, who did not show any mutation in the mentioned genes, had pathogenic copy number variations (CNVs) in SCN1A gene. These CNVs might be detected by array CGH and MLPA assay.[42,57] Marini et al. showed that deletion of 9.3 Mb (49 genes) of chromosome 2q without harming SCN1A gene could also result in Dravert phenotype.[57]

The prevalence of Unvericht-lunderborg disease or Baltic myoclonic epilepsy, a rare inherited form of epilepsy with progressive myoclonus, is higher in some regions (e.g. Sweden). This disorder has been associated with mutation of CSTB, a gene encoding cystatin B protein responsible for reducing the activity of cathepsins enzymes (protease)[58] and is inherited in an autosomal recessive (AR) pattern.[59] Furthermore, different type of gene mutations including CHRNA4 gene (frontal lobe epilepsy) have been reported in different populations.[49,50,60] It seems necessary to identify specific mutations in distinct population to provide better genetic counseling for epilepsy.[21]

There are disorders that although epilepsy is one of the symptoms, it is not the core sign. Some examples are discussed below.

Lafora body disease, a neurodegenerative disorder, is a fatal glycogen metabolism disorder with AR inheritance[61,62] and has been linked to EMP2A gene mutation (Lafarin protein).[63]

Neuronal ceroid lipofuscinoses, a cluster of at least 8 neurodegenerative disorders, a result of lysosomal storage defects and excessive accumulation of lipopigments in brain and other tissues. It has an AR pattern of inheritance.[21] CLN1 (PPT1) and CLN3 gene mutations are mainly responsible for different types of disease.[64]

Myoclonus epilepsy and ragged-red fibers are a rare mitochondrial disorder involving usually mutation of MT-TK gene located on mitochondrial DNA. It would lead to progressive neurological symptoms, including blindness and myoclonic epilepsy.[65] Mitochondrial pattern of inheritance is relatively complex (Figure 2) as maternal mutated mitochondria affects zygote formation.[66]

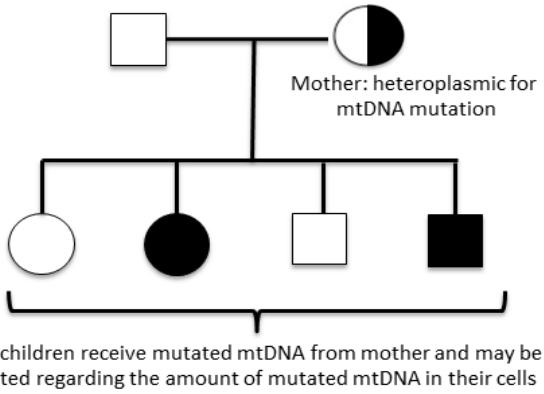


**Figure 2.** Transmission of mitochondrial DNA mutation in a hypothetical pedigree. This mode of inheritance is categorized as non-mendelian transmission because the mutated gene is not located in nuclear DNA. Mitochondria and its DNA (mtDNA) will transmit to next generation through oocyte cytoplasm so just mutated mtDNA from mother could cause the disease. Since, we have too many mitochondria and copies of mtDNA in a cell, the presence of disease and severity of its phenotype will be depended on the amount of mutated mtDNA inside individual's cells. Heteroplasmy means both mutated and non-mutated mtDNA is present in a cell. Homoplasmy means the whole mtDNAs in a cell are mutated or non-mutated

Malformation of cortical development disorders represents a major spectrum of mental disabilities with severe epilepsies caused by defective neuronal migration. Mutation of LIS1 gene encoding microtubule-associated protein is one of the several genetic defects linked to these disorders. Lissencepahly with X-link gene mutation (xLIS)[67] is another defective neuronal migration disorder that result in the lack of cerebral folds. Both genetic and non-genetic factors (e.g. viral infections of the fetus) are involved in etiology of these disorders.[68]

The introduction of new techniques of DNA sequencing has helped identifying point mutations, small insertions, and deletions.[38]

*Genetic counseling and genetic testing in epilepsy management*

Epilepsy is a multifactorial disease, and both genetic and environmental components are involved in etiology (Table 1). Various investigations, particularly twin studies, have contributed to detection the role of genetic elements in epilepsy syndromes. These findings will help predicting the clinical symptoms of the affected individual through genotype-phenotype correlation[69] and conduct follow-up of high-risk pregnancies or an infant born in a family with increased rate of epilepsy.[70] It will also aid the clinician in anticipating the clinical features in advance and manage in accordance.

Detection of specific genetic disorders will improve our understanding of the inheritance pattern. Thus, genetic counseling could better help families by estimating the risk of disease in next generation and family members of epileptic probands, who might be at greater risk for epilepsy syndromes.[69] Interestingly, the same phenotype of epilepsy in different members of a pedigree could be due to different genetic defects.[67] Consanguineous marriage will increase the risk of epilepsy syndrome, especially childhood onset of epilepsy[71-73] and is a remarkable challenge for clinicians and geneticists in societies where it is a common tradition.

## Conclusion

We emphasize on cooperation of clinicians (particularly neurologist) and medical genetic experts in eastern societies like Iran, where consanguineous marriage is a common practice. This assistance is highlighted in high-risk families. It should be noted that prior to any genetic testing, patient and family members should be pre-tested in genetic counseling sessions.[18]

The genetic testing now commercially available for epilepsy includes analysis of 70 genes for detection of point mutations and deletion/duplications using DNA sequencing, CGH array, and MLPA techniques. The specimen used for genetic testing could be whole blood or any other body tissue appropriate for DNA extraction, for example, amniotic fluid, and chorionic villi samples are required for prenatal diagnosis.

Hence, collaboration of neurologist with geneticist in the case of genetic epilepsy will help the diagnosis and in some cases will improve management[20].

## Conflict of Interests

The authors declare no conflict of interest in this study.

## Acknowledgments

We appreciate the help of our department's staff and supports of the Tehran University of Medical Sciences, Iran.

**How to cite this article:** Tafakhori A, Aghamollaii V, Faghihi-Kashani S, Sarraf P, Habibi L. Epileptic syndromes: From clinic to genetic. Iran J Neurol 2015; 14(1): 1-7.

**Table 1.** Summary of genetic abnormalities in different forms of epilepsies

| Epilepsy classification | Genetic abnormality | Genetic features | Example | Genetic test |
|---|---|---|---|---|
| Epilepsy with mendelian inheritance | Specific gene mutation | Determined mode of inheritance | Generalized myoclonic epilepsy and febrile seizures | DNA sequencing, exom sequencing |
| Epilepsy with complex inheritance | Hard to find | Mode of inheritance could not be determined | | Different tests |
| Epilepsy with chromosomal abnormality | Chromosomal aberrations | Usually sporadic | Ring chromosome 20, deletion of 6q, duplication 22q | karyotyping, CGH array, MLPA |
| Epilepsy associated with other mendelian disease | Specific gene mutation, mtDNA mutation | Determined mode of inheritance, sporadic | Lafora body disease, Neural ceroid lipofuscinoses, MERRF | DNA sequencing, exom sequencing |

MERRF: Myoclonus epilepsy and ragged-red fibers; CGH: Comparative genomic hybridization; MLPA: Multiplex ligation-dependent probe amplification

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Iranian Journal of Neurology

Original Paper

Iran J Neurol 2015; 14(1): 8-11

# The prevalence of female sexual dysfunction among migraine patients

Received: 21 Jan 2014
Accepted: 08 Aug 2014

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**Keywords**
Migraine, Female Sexual Dysfunction, Female Sexual Function Index Score

**Abstract**

**Background:** Female sexual dysfunction (FSD) defines as any disorder in the process of sexual contact including 6 main domains, desire, arousal, lubrication, orgasm, orgasm satisfaction and pain. This study was conducted to evaluate prevalence of sexual dysfunction disorder in women with migraine headache and also find the associated factors related to migraine characteristics.

**Methods:** A total of 69 eligible woman patients fulfilling criteria for migraine participated in this study. The Female Sexual Function Index (FSFI), a multi-dimensional self-report implement for appraisal of Female Sexual Function during the past month were utilized in this study. The information related to migraine including frequency, duration of headache attack, severity of headache according to visual analog scale (VAS) score and headache impact test (HIT) score were obtained using a self-administrated questionnaire.

**Results:** About 68.4% of patients had an FSFI score < 28. In domains of desire 73.7%, arousal 64.9%, lubrication 21.1%, orgasm 33.3%, satisfaction 17.5%, and pain 40.4% of patients reported some degree of dysfunction. Among variables related to migraine characteristics, only a significant association between frequency and sexual dysfunction were recorded ($P < 0.05$).

**Conclusion:** FSD is prevalent among migraine patients. The frequency of a migraine attack is associated with FSD. Serotonin mechanisms such as 5HT2, 5HT3 agonist have been hypothesized as a shared etiology for migraine and sexual dysfunction.

## Introduction

Female sexual dysfunction (FSD) defines as any disorder in the process of sexual contact, including 6 main domains, desire, arousal, lubrication, orgasm, orgasm satisfaction and pain, which cause female distress and impact their relationships with partner and their quality of life.[1,2]

The prevalence of FSD varies in a range of 43-90% in studies due to different definition, studies protocol, cultural issues, environmental factors and genetics variances.[3,4] Previous findings demonstrate that FSD is multifactorial, and there is a genetic susceptibility for sexual dysfunction that is influenced remarkably by environmental factors. Both genetic and environmental factors are involved in all dimensions of sexual function.[1,5] In recent years, Studies discuss about the significant impact of chronic pain on female sexual function. Chronic illness and chronic pain result in less sexual satisfaction and cause some degree of sexual dysfunction.[6,7]

Primary headache especially migraine is a common cause of chronic pain and temporary disability.[8] The prevalence of migraine and chronic headache in women is respectively 17.1% and 4%.[9-10] Gal Ifergane in his investigation on a student sample showed that a migraine suffers have a higher sexual pain, and satisfaction disorder compared with control subjects.[11]

Bestepe et al. assessed sexual function among



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headache suffers using Arizona sexual experiences scale (ASEX score) and concluded that migraineurs have more difficulties with vaginal lubrication and achieving orgasm in comparison to normal samples.[12] In a large population based study in United States, the frequency and quality of sexual relationships were affected in 86% of migraine suffer, and resulted in divorce in 26% of cases.[13]

This study is conducted to evaluate the prevalence of sexual dysfunction disorder in women with migraine headache in Iran.

## Materials and Methods

We designed a cross-sectional study to assess sexual function in women under treatment and follow-up for migraine. Our aim was to investigate the prevalence of female sexual function disorder among migraineur patients and also to identify the associated factors of FSD including headaches characteristics.

The study was conducted between April and June 2013 in a headache clinic center.

The Ethics Committee of the Tehran University of Medical Sciences approved the study. Informed consent was obtained from the patients.

Eighty-eight women with complain of headache consecutively were interviewed to participate in this study. The patients enrolled in this study met the International Classification of Headache Disorders criteria for migraine and had a sexual partner for a minimum period of last 1 year**.** 69 eligible patients were recruited.

A detailed history of headache attacks characteristics were obtained in an interview of an expert neurologist with patients. Our interview includes questions for disease duration, severity and frequency of headache attacks and attack duration. The severity of headache attacks was estimated based on visual analog scale (VAS) score. The impact of headache on quality of life was evaluated with headache impact test (HIT) score questionnaire. The Female Sexual Function Index (FSFI), a multidimensional self-report implement for appraisal of Female Sexual Function during the past month, were utilized in this study. This questionnaire consist of 19 questions in six main domains of sexual function including sexual desire, sexual arousal, vaginal lubrication, ability to achieve orgasm, orgasm satisfaction and pain and rated on a 5 points scale and full score range from 2 to 36. The cut-off point for the scale was found to be 28 in Iranian translated draft of FSFI questionnaires (sensitivity = 83% and specificity = 82%).[14] Details about subscale cut-off point is presented in table 1.

SPSS software (version 18, SPSS Inc., Chicago, IL, USA) were applied to describe the sexual function status of subjects. Independent t-test was administrated to compare HIT Score, frequency and VAS Score in two subgroups of migraineurs regarding patients with or without FSD. $P \leq 0.05$ was considered to be significant.

**Table 1.** Female sexual function and subscale scoring and cut-off points

| | Domain | Questions | Factor | Cut-off point |
|---|---|---|---|---|
| FSFI | Desire | 1, 2 | 0.6 | 3.3 |
| | Arousal | 3, 4, 5, 6 | 0.3 | 3.4 |
| | Lubrication | 7, 8, 9, 10 | 0.3 | 3.7 |
| | Orgasm | 11, 12, 13 | 0.4 | 3.4 |
| | Satisfaction | 14, 15, 16 | 0.4 | 3.8 |
| | Pain | 17, 18, 19 | 0.4 | 3.8 |
| | | Total | | 28 |

FSFI: Female sexual function index

## Results

Of the 69 migraineur women who were interviewed, 12 (17%) were excluded from the analysis because of significant missing data. Average age of the migraine patients in the analysis sample was 38.11 ± 9 years (range 15-57). About 68.4% of migraine patients reported FSF score under the validated cut-off (< 28). Most common sexual dysfunction in migraine patients were observed in domains of desire and arousal (73.7 and 64.9%, respectively) (Figure 1).

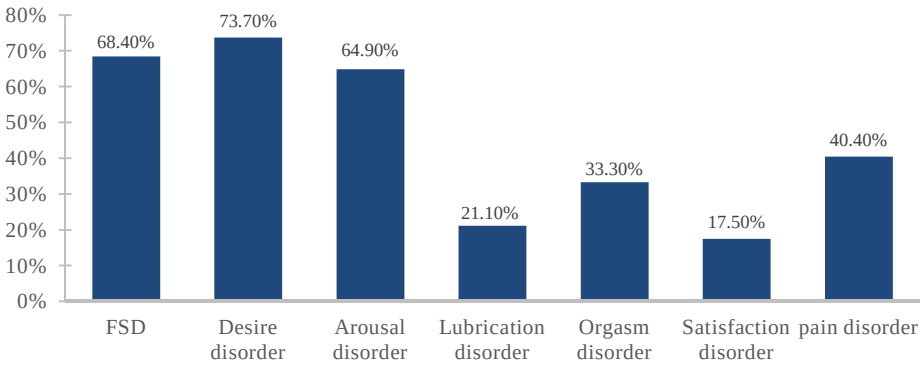


**Figure 1.** Prevalence of subscales of sexual dysfunction in female migraine patients
FSD: Female sexual dysfunction

**Table 2.** Comparison of variable between two subgroups of migraine patients regarding with or without female sexual dysfunction (FSD)

| Variables | Normal sexual function group | Sexual dysfunction group | P |
|---|---|---|---|
| Age (year) | 6.52 ± 32.73 | 14.65 ± 36.44 | 0.42 |
| Disease (year) | 4.71 ± 8.55 | 10.37 ± 11.6 | 0.18 |
| Pain intensity (VAS score) | 1.85 ± 7.36 | 2.21 ± 7.57 | 0.78 |
| 30-day headache frequency | 3.46 ± 4.27 | 7.92 ± 8.20 | 0.04 |
| HIT score | 5.98 ± 62.73 | 18.87 ± 57.62 | 0.38 |
| Attack duration (%) | | | |
| > 12 h | 40 | 38.9 | 0.94 |
| < 12 h | 60 | 61.1 | |

VAS: Visual analog scale; HIT: Headache impact test

Based on our analysis of subgroups of migraine patients, a positive association was revealed between FSFI score and headache frequency (P = 0.04).

No significant association was detected between FSD and age, VAS score, migraine duration years and hit score (P > 0.05) (Table 2).

## Discussion

FSD is an important issue for many of women that disturb their emotional relationship with their partner and also impair their quality of life. Especially in migraine patients is very important to study the prevalence of FSD and assess the factors that increase its probabilities. A general population-based study in Iran estimated FSD in 31.5% of subjects[15] obviously FSD was meaningfully more common in our migraine patients compared to general population but less common than result of Nappi et al. study in migraine and tension patients(68.4 vs. 90%).[4] This substantial differences may reflect medical, psychological factors, socioeconomic, cultural and the characteristic of samples. Desire and Arousal disorder were the most common subscale of sexual dysfunction in migraine patients (73.7 and 64.9% respectively). In agreement with our findings, other studies in general population have reported that desire is the most common impaired domain of sexual dysfunction.[15,16] Mostly the chronic pain disorders can adversely influence sexual desire and activity over the time.[6,7] Gal Ifergane believed that avoidance, fear of sex and as a result lower satisfaction are associated with higher levels of sex pain disorder.[11] The comorbid disorders especially depression can disturb neuroendocrine balance, which have some roll in sexual derive and satisfaction.[17]

Some data explain the possible role of serotonin receptors in migraine and sexual dysfunction. A shared mechanism which can suggest these association are role of 5-HT2 and 5-HT3.[18-24] Some trials showed that anti receptors of 5-HT2 and 5-HT3 such as mirtazapine can be recommended as therapeutic agents for sexual dysfunction.[25,26] To our knowledge there are not sufficient studies that examined the association of headache characteristics and sexual dysfunction. Consistent with our findings Bestepe et al. found no significant association between headache duration, severity and sexual dysfunction.[12] However, dissimilar to findings of Bestepe et al.[12] and Maizels and Burchette[27] our data analysis detected a significant association between frequency of a migraine attack and sexual dysfunction.

The result of this study invite other researcher to conduct such studies with more sample size and more precise design and also offer a background of this issue to physician and help them to have more comprehensive attitude while interviewing the patients with complaint of migraine in clinic.

## Conflict of Interests

The authors declare no conflict of interest in this study.


## Acknowledgments

We would like to express our deep gratitude to Ms. Jabbari for her assistance with the collection of our data. We would also like to extend our thanks to the Neurology Ward of Sina Hospital for offering us the resources to perform this project.



**How to cite this article:** Abdollahi M, Toghae M, Raisi F, Saffari E. The prevalence of female sexual dysfunction among migraine patients. Iran J Neurol 2015; 14(1): 8-11.


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Iranian Journal of Neurology

Original Paper

Iran J Neurol 2015; 14(1): 12-16

# A novel effect of Noscapine on patients with massive ischemic stroke: A pseudo-randomized clinical trial

Received: 17 Dec 2013
Accepted: 22 May 2014

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**Keywords**
Noscapine, Massive Ischemic Stroke, Treatment, Clinical Trial

**Abstract**

**Background:** Massive ischemic stroke causes significant mortality and morbidity in stroke patients. The main treatments for massive ischemic stroke are recombinant tissue plasminogen activator (rtPA), craniotomy, and endovascular interventions. Due to destructive effects of bradykinin on the nervous system in ischemic stroke, it seems reasonable that using Noscapine as a Bradykinin antagonist may improve patients' outcome after ischemic stroke. The effect of Noscapine on massive ischemic stroke was shown by the previous pilot study by our group. This pseudo-randomized clinical trial study was designed to assess the result of the pilot study.

**Methods:** Patients who had clinical symptoms or computed tomography scan indicative of massive stroke (in full middle cerebral artery territory) were entered to the study. The cases received the drugs according to their turns in emergency ward (pseudo-randomized). The patient group received Noscapine, and the control group received common supportive treatments. The patients and data analyzer were blinded about the data. At the end of the study, to adjust confounding variables we used logistic regression.

**Results:** After 1-month follow-up, 16 patients in the control group and 11 patients in the case group expired (P = 0.193). Analyzing the data extracted from Rankin scale and Barthel index check lists, revealed no significant differences in the two groups.

**Conclusion:** Despite the absence of significant statistical results in our study, the reduction rate of 16% for mortality rate in Noscapine recipients is clinically remarkable and motivates future studies with larger sample sizes.

## Introduction

Although the stroke is the third cause of death in the world but its treatment is limited to recombinant tissue plasminogen activator (rtPA) and mechanical methods (arterial recanalization). Using these methods needs special settings, and the time of their administration is limited. Furthermore, some countries do not afford these treatments.[1-3]

The neuroprotective treatments have been proved to be effective in animal models, but the trials have not proved these effects in the human being.[4-8]

Noscapine is an alkaloid microtubule binding agent initially derived from the opium plant, but it does not have sedative, euphoric, palliative, and respiratory depressant effects.[9] This novel substance has been used as a cough suppressant.[10] Noscapine is taken orally and can cross blood brain barrier easily.[7] The antitussive activity is attributed to central mediated mechanisms.[11]



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Bradykinin is an autacoid substance that exists physiologically in the body.[12] This substance induces arterial dilation through direct effect on muscular layer and indirectly by releasing the endothelial derived releasing factors such as nitric oxide and prostaglandin $I_2$. It has an adverse effect on veins and causes venous constriction. It also stimulates edema and inflammation.[12] In a previous study, it was shown that the Noscapine inhibits the contractive effect of bradykinin in pig's intestine and rat's vasodefran.[13] It was hypothesized that the antitussive effect of the drug is due to suppression of bradykinin (FR190997).[14]

Microtubule binding agents also have anti-angiogenic activity by disrupting the endothelial tubule formations. Noscapine inhibits vascular endothelial growth factor (VEGF) and suppress neovascularization. The mechanism of reducing the neovascularization was suggested by Newcomb et al.[15]

Due to the inflammatory and destructive effects of bradykinin in ischemic stroke, it seems reasonable that using Noscapine as a Bradykinin antagonist may improve patients' outcome after ischemic stroke. The drug's effect on reducing mortality rate of mice with cerebral injuries secondary to hypoxic-ischemic attack, and also on reducing the mortality rate of patients with large acute ischemic stroke in a pilot study,[16] asserts designing the new study with larger sample size to understand whether Noscapine is effective on mortality rate of patients with acute massive ischemic stroke.

## Materials and Methods

This study was conducted in the review board of the Tehran University of Medical Sciences, Iran, and the ethical approval was confirmed by Iranian Registry of Clinical Trials. This is a Primary Registry in the World Health Organization (WHO) Registry Network with the help from the Ministry of Health and Medical Education. The study was performed at Rasoul-e-Akram Hospital, one of the main referral neurology centers of Tehran. All researchers respected to patients' data and the declaration of Helsinki. The authors did not have any conflict of interests in this study.

This study was a pseudo-randomized clinical trial that was conducted paralleled.

The patients with a diagnosis of large ischemic stroke both clinically and by neuroimaging [brain computed tomography (CT) scan] were entered to the study .We defined large ischemic strokes as strokes with involvement of total middle cerebral artery territory. The patients with normal initial CT scans underwent the second CT scan 24 h after the first one. If the diagnosis was not confirmed, the patient was excluded from the study.

Patients with modified Rankin scale > 2 before the presentation of ischemic stroke were excluded from the study. Other expressed inclusion and exclusion criteria were considered prior to the initiation.

Inclusion criteria were defined as the age of 18 years old and older; the interval of 12 h or less from symptom onset to admission and the level of consciousness > 2; limb movement > 7 and the total score > 7 by assessing the National Institutes of Health Stroke Scale (NIHSS).[17]

Since at the time of the study rtPA was not used in our center for stroke patients, none of the patients in case or control group received rtPA.

Exclusion criteria were defined as modified Rankin scale more than 2 before the presentation of stroke, relief of neurologic defects within the first minutes, ,suspicious of septic meningitis or subarachnoid hemorrhage or neurologic defects caused by seizures and could not be differentiated from Todd's phenomenon. Also patients with probable or confirmed brain masses, congestive heart failure, renal or liver diseases, proliferative retinopathy, cancer, head trauma, mandatory mechanical ventilation, unstable vital signs and psychological disorders which interfered with mental state evaluation were all excluded from the study.

In this study, allocation was based on a pseudo randomization process in which patients with odd numbers considered as the control group and the others with even numbers received the novel drug added to the routine regime (based on their consecutive assigned number in emergency ward). The patient group received Noscapine and common supportive treatments, and the control group received only common supportive treatments. The data analyzer was completely blinded to the treatment strategies. Noscapine was used as syrup in conscious patients and via nasogastric tube in unconscious patients. The syrup was made by Capval-saft Company, Germany. The applied dosage was considered 50 mg/three times a day for 5 days. The dosage was assimilated to the previous dosage used in patients with coughing.

To evaluate the patients we used:

1. Brain CT scan for confirmation of massive ischemic stroke
2. Physical examination for the diagnosis of ischemic stroke and filling out the NIHSS at the emergency ward, 1 week and 1 month after receiving the drugs.
3. The checklists of Rankin scale and Barthel index for evaluating functional disabilities 1 week after receiving the drugs.[18]

Though the main aim of this study was comparing the mortality rate in patients with massive ischemic

stroke who received Noscapine with those who received usual drugs, the mortality rate was estimated after 1 month.

Sampling was performed conveniently in the patients with the diagnosis of massive brain ischemic stroke. According to the previous studies, α and β error were considered 0.05 and 0.1 respectively. By using sampling tests, the number of cases was estimated 16 in each group, but for increasing the power of the study the sample size was considered 30 in each group.

The data were entered to the SPSS software (version 18, SPSS Inc., Chicago, IL, USA). For comparing the qualitative variables such as mortality rate in the two groups, we used chi-square test. For comparing the disability scores, Rankin scale, and Barthel index, if the data were distributed parametrically, we used student's T-test or its non-parametric equivalent (Mann–Whitney U-test). Logistic regression was applied on parameters with significant or near significant differences for further adjustment.

## Results

The study included 30 patients in each group and none of them were excluded during the study; whereas, 13 of them in the case group and 14 of them in the control group were men. Case group was defined as the patients who received Noscapine. The mean age in the case and control group was 69.5 ± 4.34 and 71.1 ± 4.97 years old, respectively.

Among Noscapine recipients, the left brain hemisphere was involved in 16 patients and right hemisphere in 14 patients. In the control group, the left hemisphere was involved in 13 patients and right hemisphere in 17 patients. The prevalence of demographic characteristics and some initial risk factors in each group is illustrated in table 1. The analysis of these risk factors revealed no significant differences between the two groups.

After 1 month follow-up, 16 patients (53%) in the control group and 11 patients (37%) in the case group expired. The chi-square test revealed no significant difference between the two groups (P = 0.193).

Further adjustment analysis by logistic regression showed no significant different in mortality rate between the two groups (Table 2).

Of all 60 patients, pneumonia was seen in 11 cases, ischemic heart attack in 8, cardiac arrhythmia in 3, deep vein thrombosis in 2, brain herniation in 1, gastrointestinal bleeding in 1, and diabetic ketoacidosis in 1 case were the main causes of patients' death at the end of the study.

Analyzing the data extracted from Rankin scale and Barthel index check lists, revealed no significant differences between the two groups (Table 3).

## Discussion

Although the previous pilot study in patients with massive ischemic stroke revealed significant decrease in mortality rate in Noscapine recipients,[16] our study with larger sample size did not show any significant difference between the two groups. Further, analyses from the Rankin scale and Barthel index check lists showed the drug could not reduce the morbidity in these patients.

In studies performed in 1992 and 2004, it was shown that radiolabeled Noscapine crosses the blood-brain barrier and binds to the neurons of the central nervous system.[19]

Hitherto, the anticancer/anti-proliferative effect of Noscapine has been discussed. The drug increases microtubules pause phase and also induces apoptosis through mitochondrial pathways.[8,9,20-22] Suppressing microtubule dynamics without the disturbing microtubule polymer figure reduces toxic effects on normal tissues while the anticancer activity retains.[10,22] Although specific side-effect has not been reported noticeably, chest pain was reported in one article.[23]

**Table 1.** Demographic characteristics

| Characteristic | Control group (%) | Noscapine group (%) | P |
|---|---|---|---|
| Age | | | |
| Range | 48-85 | 38-90 | 0.347 |
| Mean | 71.0 | 69.5 | 0.521 |
| Female | 53.0 | 43.5 | 0.347 |
| Male | 47.0 | 56.5 | 0.212 |
| HTN | 53.4 | 63.4 | 0.432 |
| Smokers | 23.3 | 13.3 | 0.314 |
| Previous stroke | 26.7 | 20.0 | 0.541 |
| HLP | 6.7 | 3.3 | 0.550 |
| Diabetics | 36.7 | 26.7 | 0.404 |
| IHD | 46.6 | 30.0 | 0.183 |
| AF | 26.7 | 20.0 | 0.541 |
| MS | 3.3 | 13.3 | 0.814 |

HTN: Hypertension; HLP: Hyperlipidemia; IHD: Ischemic heart disease; AF: Atrial fibrillation; MS: Mitral stenosis

**Table 2.** The relationship between mortality rate and different risk factors

| Factors | Dead | Alive | P |
|---|---|---|---|
| Sex | | | |
| Male | 15 | 12 | 0.938 |
| Female | 18 | 15 | |
| HTN | | | |
| + | 15 | 10 | 0.511 |
| - | 18 | 17 | |
| DM | | | |
| + | 21 | 20 | 0.387 |
| - | 12 | 7 | |
| IHD | | | |
| + | 21 | 16 | 0.729 |
| - | 12 | 11 | |
| CVA | | | |
| + | 24 | 22 | 0.425 |
| - | 9 | 5 | |
| HLP | | | |
| + | 31 | 26 | 0.687 |
| - | 2 | 1 | |
| AF | | | |
| + | 26 | 20 | 0.668 |
| - | 7 | 7 | |
| Smoking | | | |
| + | 25 | 24 | 0.191 |
| - | 8 | 3 | |
| MS | | | |
| + | 30 | 24 | 0.814 |
| - | 3 | 2 | |

HTN: Hypertension; DM: Diabetics mellitus; IHD: Ischemic heart disease; CVA: Cerebrovascular accidents; HLP: Hyperlipidemia; AF: Atrial fibrillation; MS: Mitral stenosis

**Table 3.** Functional (Barthel index) and disability (Modified Ranki scale) outcomes after 1 month

| Functional and disability outcomes | Control group | Noscapine group |
|---|---|---|
| a. Barthel index (%) | | |
| 95-100 | 0 | 0 |
| 55-90 | 0 | 1 (3.4) |
| 0-50 | 16 (53.4) | 18 (60.0) |
| Died | 14 (46.6) | 11 (36.6) |
| b. Modified Rankin scale (%) | | |
| 0-1 | 0 | 0 |
| 2-3 | 0 | 4 (13.4) |
| 4-5 | 16 (53.4) | 15 (50.0) |
| Died | 14 (46.6) | 11 (36.6) |

An in vitro study in 2008 planned for assessing the neuro-protective potential of Noscapine that demyelinating effect of vincristine used in patients with acute lymphoblastic leukemia was decreased when Noscapine was added to the regime.[7]

Electrically induced coughs that mimic the medicine induced coughs are relatively suppressed by Noscapine, by means of affecting autonomic nervous system.[11]

Newcomb et al. showed that Noscapine disrupts the functional pathway of hypoxia-inducible factor-1 (HIF-1) in tumors especially glioma. They also demonstrated that these effects are accompanied by inhibition of HIF-1α expression that leads to decreased secretion of VEGF.[15]

Landen et al., in 2004, showed that Noscapine hinders the growth of a highly aggressive mouse glioma. They revealed that Noscapine may be a novel hope for treating aggressive glioma that does not respond to chemotherapy.[19]

In another study in Iran, in 2003, it was shown that mice's brain edema was significantly reduced by Noscapine.[14]

In our study, although the risk factors (diabetes mellitus, ischemic heart disease, previous ischemic stroke, hyperlipidemia, atrial fibrillation, and smoking) were not completely matched between the

two groups but using logistic regression for adjustment, there revealed no significant difference between mortality rates between groups.

Although the location of the study, the company of the medicine, and the inclusion and exclusion criteria in this study were similar to the previous pilot study, the result was different. Unlike the previous pilot study, we did not find any significant correlation between atherosclerosis risk factors, the involved hemisphere and the demographic factors such as age and sex with the mortality rate in the groups. According to the differences between the studies, future evaluations with more sample size are recommended.

Despite the absence of significant decrease in mortality rate in the Noscapine group, the reduction rate of 16% for mortality rate in Noscapine recipients (comparing to the control group) is clinically remarkable and motivates future studies with larger sample size for providing the higher power of study. Also, placebo usage in the control group is recommended.

## Conclusion

Massive ischemic stroke causes significant mortality and morbidity among stroke patients. Despite using rtPA, craniotomy and endovascular interventions for these patients, there is neither an effective neuroprotective nor an antiedema agents in these patients. Noscapine as an antibradykinin agent can be a potential candidate for decreasing brain edema, enhancing neuroprotection and thus reducing the mortality and morbidity of ischemic stroke. Although our study didn't show a decrease in mortality rate among Noscapine recipients with massive ischemic stroke, further studies with larger sample volumes are needed to show the effects of this substance.

## Conflict of Interests

The authors declare no conflict of interest in this study.


## Acknowledgments

We would like to thank all patients who have participated in our study, and the neurology ward staff in Rasoul-e-Akram Hospital.

**How to cite this article:** Mahmoudian M, Rezvani M, Rohani M, Benaissa F, Jalili M, Ghourchian Sh. A novel effect of Noscapine on patients with massive ischemic stroke: A pseudo-randomized clinical trial. Iran J Neurol 2015; 14(1): 12-6.


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Iranian Journal of Neurology

Original Paper

Iran J Neurol 2015; 14(1): 17-21

# Serum 25(OH) Vitamin D levels is not associated with disability in multiple sclerosis patients: A case-control study

Received: 05 Mar 2014
Accepted: 21 Aug 2014

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**Keywords**
Serum 25(OH) vitamin D level, Disability, Multiple sclerosis

**Abstract**

**Background:** It seems that serum vitamin D levels are one of the potential environmental factors affecting the severity of multiple sclerosis (MS). In this study, we aim to evaluate vitamin D levels in MS patients and healthy subjects and assess the relationship between vitamin D level and disability.

**Methods:** In this case-control study, 168 rapid relapsing MS patients and 168 matched healthy controls were randomly included in this study. Demographic characteristics and serum vitamin D levels for patients and controls, as well as expanded disability status scale (EDSS), duration of disease and diagnostic lag for patients were evaluated. We followed up patients for 6 months and relapses were recorded.

**Results:** The mean serum vitamin D levels were 19.16 ± 17.37 inpatients and 25.39 ± 19.67 in controls (P = 0.560). The mean serum vitamin D levels were 12.65 ± 13.3 in patients with relapses and 22.08 ± 18.22 in patients without any relapses (P < 0.001). There was no significant correlation between EDSS score and serum vitamin D levels (r = −0.08, P = 0.280). There was a significant positive correlation between EDSS score and disease duration (r = 0.52, P < 0.001).

**Conclusion:** In conclusion, vitamin D level in patients with MS was significantly lower than the healthy subjects, but no significant relationship was found between vitamin D levels and disability. Our findings did not suggest a protective role for serum vitamin D levels against disability.

## Introduction

Multiple sclerosis (MS) is one of the most common neurological diseases affecting adults.[1] It is regarded as a chronic, inflammatory autoimmune disease of the central nervous system, with serious debilitating effects, which result in extensive and major economic and social impressions.[2-6] MS has either a progressive or relapsing-remitting (RRMS) nature and manifests as acute focal inflammatory demyelination causing axonal damages.[2,6] It usually involves young adults (20-40 years old) and has a twofold influence on women compared with men.[7,8]

There is a probable autoimmune etiology for MS, but it seems that genetic and environmental factors have an equal role in constructing the final clinical picture.[9] Vitamin D deficiency, which seems to be a risk factor for some systemic diseases such as lupus erythematous,[10] has been known to be modifiable risk factor for MS[11] and recent studies suggests that vitamin D is an important environmental factor affecting the disease.[12] On the other hand, the prevalence of MS is variable in different degrees of latitude, with a higher prevalence of the disease in high-latitude areas and vice versa. This variety is believed to be due to ultraviolet (UV) light exposure and subsequent change in vitamin D synthesis,[13] as



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the dominant source of vitamin D for most people is through skin exposure to sunlight.[14]

There have been some inconsistent reports in regards to different 25(OH) vitamin D serum levels in MS patients and community controls[15-21] and the relation of vitamin D levels and disease severity, relapse rate and disability.[6,17,22-24] It has been shown in some studies that high levels of 25(OH) vitamin D is related with lower risk of relapsing and lower disability expressed as expanded disability status scale (EDSS) score.

There are some reports about increasing incidence of MS in Middle Eastern countries, including Iran.[25-28] The incidence of MS has been increased from 3.64 person per 100000 population in 2007 to 9.1 person per 100000 population in 2009.[26] Considering the relatively high prevalence of MS in Iran,[29,30] higher latitude in North West of Iran than other provinces and uncertainty about the role of serum vitamin D levels in the severity of MS, we conducted this study to compare the serum level of 25-hydroxy vitamin D in MS patients with healthy controls and to investigate its potential relation with disability and relapse rate in our patients.

## Materials and Methods

This case–control study was designed and performed in the Neurology Department of Razi Hospital, Tabriz University of Medical Sciences, Tabriz, Iran. Between June 2012 November 2012, 168 definitive MS patients of East Azarbaijan MS society with RRMS were enrolled in the study. RRMS was confirmed by clinical findings and magnetic resonance imaging. Inclusion criteria were disease duration based on the initiation of symptoms for at least 6 months, being in the remission phase without any history of a new attack in the last month, no history of diseases related to vitamin D deficiency and no intake of drugs or supplements containing vitamin D in last 30 days.[31] One hundred and seventy-five healthy controls from Razi and Imam Reza Hospitals staff matched for age, gender and time and date of blood sampling were included in the study. Only those patients and healthy subjects were evaluated with available follow-up data. Informed consent was obtained from all participants. Blood samples were obtained after an overnight fasting and were measured by chemiluminescent immunoassay method for 25(OH) vitamin D levels, all in the same laboratory. Demographic characteristics, including age and gender, family history of MS in first and second degree family members, duration of disease from the first symptoms presentation, diagnostic lag, EDSS score and relapse rate were recorded by one neurologist. After taking blood samples, patients were followed up monthly for 6 months by phone calls and relapses were recorded based on both patients self-reports and medical documentation. We excluded patients whom we were unable to contact in follow-up period. Corresponding controls were excluded too. We defined Vitamin D deficiency, insufficiency, and normal status as 25(OH)D levels < 10 ng/ml, between 10 and 30 ng/ml and more than 30 ng/ml, respectively.

Statistical analyses were performed using the SPSS for Windows (version 17.0, SPSS, Chicago, Illinois, USA). Quantitative data were presented as mean ± standard deviation, whereas qualitative data were demonstrated as frequency and percent (%). Demographic data, clinical parameters and laboratory values of the patients were compared with controls, using the chi-square and Student's t-test methods, as appropriate. Pearson's correlation analysis was used to determine the relationship between serum vitamin D levels and duration of disease, EDSS score, diagnostic lag and age. A $P < 0.050$ was considered as significant.

## Results

In this study, a total of 168 MS patients and 168 matched controls for age and sex were studied. The demographic and clinical characteristics of both groups are summarized in table 1. RRMS patients had significantly lower serum vitamin D levels, higher vitamin D deficiency and less Regular full-time jobs compared to healthy controls. In RRMS patients, mean duration of disease (from first symptoms initiation) and diagnostic lag were 7.41 ± 4.80 and 1.32 ± 1.92 years respectively in patients. Mean EDSS was 2.83 ± 1.18 and mean relapse rate in the 6 months follow-up period was 1.28 ± 0.45 in patients. Fifty-two patients (31%) had at least one episode of relapse in a 6 months period after taking blood samples.

**Table 1.** Demographic and clinical characteristics of patients and controls

| Characteristics | Patients (n = 168) (%) | Controls (n = 168) (%) | P |
|---|---|---|---|
| Female (%) | 131 (78) | 127 (75.6) | 0.880 |
| Age* | 33.6 ± 7.69 | 34.43 ± 7.31 | 0.620 |
| Serum Vitamin D* | 19.16 ± 17.37 | 25.39 ± 19.67 | 0.002* |
| Vitamin D status | | | |
| Deficiency | 80 (47.62) | 49 (29.17) | |
| Insufficiency | 53 (31.55) | 68 (40.48) | 0.002* |
| Normal | 35 (20.83) | 51 (30.35) | |

P is two-sided significant; *Numbers are provided as mean ± standard deviation

**Table 2.** Demographic and clinical characteristics of patients with and without relapses in follow up period

| Variable | Relapses (52) | No relapses (116) | P |
|---|---|---|---|
| Female (%) | 41 (78.8) | 90 (77.6) | 0.850 |
| Family history of MS | 13 (25) | 26 (22.4) | 0.710 |
| Serum Vitamin D* | 12.65 ± 13.30 | 22.08 ± 18.22 | < 0.001* |
| Age* | 34.09 ± 6.92 | 33.37 ± 8.03 | 0.570 |
| EDSS* | 3.00 ± 0.76 | 2.75±1.33 | 0.240 |
| Disease duration*,** | 7.56 ± 4.65 | 7.42 ± 5.16 | 0.670 |
| Diagnostic lag*, *** | 1.63 ± 2.29 | 1.18 ± 1.72 | 0.160 |

P is two-sided significant; * Numbers are provided as mean ± standard deviation; ** Duration of disease from the first symptoms presentation; *** Delay between symptoms presentation and definite diagnosis; EDSS: Expanded disability status scale

**Table 3.** Correlations between independent variables and expanded disability status scale (EDSS)

| Variable | Coefficient | P |
|---|---|---|
| Sex | -0.05 | 0.440 |
| Age | 0.29 | < 0.001* |
| Serum vitamin D | -0.08 | 0.280 |
| Disease duration | 0.52 | < 0.001* |
| Diagnostic lag | 0.19 | 0.010* |

* P < 0.050 is considered significant

RRMS patients were divided into with and without relapse (Table 2). There was no difference between two groups regarding the age, gender, family history of MS, EDSS score, disease duration and diagnostic lag. However, serum vitamin D levels were significantly lower in patients with relapse compared with no relapse patients. Although serum vitamin D levels were insignificantly lower in female patients (20.09 ± 18.23 in males and 18.9 ± 17.19 in females), but there was no difference between male and female patients regarding to parameter studied such as, EDSS score and diagnostic lag.

Table 3 demonstrates the correlation between quantitative values and EDSS. There was significantly positive correlation between age, disease duration and diagnostic lag with EDSS. We observed no significant correlation between EDSS score and serum vitamin D levels and patients' gender.

We also compared vitamin D levels between genders in two groups. Serum 25(OH)D was slightly lower in female patients and controls compared to males, but this difference was not statistically significant (20.09 ± 18.23 in males and 18.9 ± 17.19 in females (P = 0.710) in cases and 29/87 ± 20.48 in males and 25.2 ± 19.12 in females (P = 0.210) in control group).

## Discussion

MS risk associated with low vitamin D levels might vary between ethnicities and regions with different latitude; For example, it was reported that the MS risk significantly decreased with increasing 25(OH)D serum levels in Caucasians, whereas no significant associations between 25(OH)D levels and MS risk were found among Africans and Hispanics.[11] Furthermore, there is some inconsistency between different reports; Correale et al.[19] evaluated serum 25(OH)D levels between Spanish MS patients and healthy controls and reported a significant lower serum 25(OH)D levels compared to control group. In contrast to this study, Kragt et al.[20] followed up MS patients and healthy subjects for a year by performing a large cohort in The Netherlands and reported no difference between two groups throughout the whole follow up period.

To the best of our knowledge, no study has been carried out in Northwestern of Iran. In this study, we investigated levels of serum vitamin D in MS patients and compared it with matched healthy controls. We also studied possible correlation between the severity of the disease (EDSS score) and other evaluated parameters. Findings of this study suggest that serum Vitamin D levels are significantly lower in MS patients compared to healthy subjects, but there is no correlation between this laboratory finding and disease's severity. We found that there is a significant positive correlation between EDSS score and patients' age and disease duration.

Our results had some similarities and differences to recent findings. Similar to most of previous studies[19,21,22,31,32] and unlike Kragt et al.[20] and van der Mei et al.[17] we found that serum vitamin D levels are significantly different between patients and matched control. Regarding to substantial strength given to the hypothesis and higher latitude and lower temperature of North Western of Iran compared to equatorial regions[17] and central provinces of Iran[21] and overlooking the different criteria used in various studies to define vitamin D deficiency and insufficiency, it seems that vitamin D deficiency is an important phenomenon in MS patients which may

occur due to different reasons such as decreased outdoor activity and exposure to UVB sunlight, as the role of sunlight exposure in vitamin D synthesis is definitive.[33]

In this study, serum 25(OH)D was slightly lower in female patients and controls compared to males that can be due to heavier cloth cover used by female ones in Iranian society. Moreover, it must be noted that some of these differences may be as a result of non-fasting sampling and different methods for measuring serum vitamin D,[17] low recruited participants[16,18] and unmatched groups.[20]

Our results showed that there is no significant correlation between EDSS and serum vitamin D levels. Most of the recent efforts show that EDSS is directly correlated with serum vitamin D levels. van der Mei et al.[17] studied 127 MS patients and showed that patients with EDSS more than 3 are more likely to have lower vitamin serum concentrations. Smolders et al.[23] reported a significant positive correlation between EDSS and serum vitamin D levels. Harandi et al.[34] studied 78 Iranian MS patients and reported such relationship between theses to parameters only in female patients. Unlike these studies, Yildiz et al.[35] and Hatamian et al.[24] didn't present any significant relation between EDSS and serum vitamin D status. They presumed small study population as a probable reason for an insignificant relation. Considering large study population in this survey, different skin types, exact geographical location, socioeconomic status, lower disease duration and EDSS score compared to other studies and genetic variation are potential factors affecting this correlation. Although it is reported that replacement supplement therapy has equal effect as placebo therapy on EDSS score and relapse rate in MS patients, but it looks that vitamin D replacement in these patients should be considered in their therapeutic and follow up plan and despite their disability, it can be beneficial for their resistance to mechanical traumas and reducing fractures that could affect patient's outdoor activity and sunlight exposure.

## Conclusion

Vitamin D level in patients with MS was significantly lower than the healthy subjects, but no significant relationship was found between vitamin D level and disability.

## Conflict of Interests

The authors declare no conflict of interest in this study.


## Acknowledgments

This research was financially supported by Tabriz Neurology Research Center, Tabriz University of Medical Sciences, Iran. The authors have no conflicts of interest.



**How to cite this article:** Nikanfar M, Taheri-Aghdam AA, Yazdani M, Shaafi Sh, Masoudian N, Akbari H, et al. Serum 25(OH) Vitamin D levels is not associated with disability in multiple sclerosis patients: A case-control study. Iran J Neurol 2015; 14(1): 17-21.


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Iranian Journal of Neurology

Original Paper

Iran J Neurol 2015; 14(1): 22-28

# Comparison of endovascular coiling and surgical clipping for the treatment of intracranial aneurysms: A prospective study

Received: 21 Feb 2014
Accepted: 3 Aug 2014

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**Keywords**
Aneurysm, Intracranial, Therapy, Assessment, Outcome

**Abstract**

**Background:** Management of intracranial aneurysms has made debates about the best treatment modality in recent years. The aim of this study was to compare the interventional outcomes between two groups of patients, one treated with endovascular coiling and the other treated with surgical clipping.

**Methods:** This prospective study included 48 patients with intracranial aneurysms who underwent endovascular coiling (27 patients) or surgical clipping (21 patients) from July 2011 to August 2013. A neurologist examined patients in admission and followed them by phone call 1-year after intervention.

**Results:** Mean modified Rankin Scale (MRS) score at the time of admission in endovascular group was 2.86 ± 0.974 whereas it was 3.81 ± 1.078 in surgical clipping group (P = 0.0040). Focal neurologic signs were higher in clipping during procedures (P = 0.0310). Of 37 patients who followed up for a year, 19 were in endovascular group and 18 in surgical clipping group. At 1 year follow-up, MRS improvement was statistically significant in coiling group (P = 0.0090), but not in clipping group (P = 0.8750). Mean difference of MRS score at the time of admission and at one year later, was 0.947 ± 1.224 in endovascular group and 0.111 ± 2.083 in surgical group (P = 0.3000).

**Conclusion:** There was no statistically significant difference at 1 year outcome between two groups. We recommend further interventional studies with larger sample sizes for better evaluation of the modalities.

## Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a disastrous and fatal medical emergency requiring immediate intervention as approximately 12% of patients die before receiving medical supports, 33% within 48 h and 50% within 30 days of aSAH and 50% of survivors suffer from permanent disability and dependency.[1] Endovascular coiling has increasingly become an alternative procedure for surgical clipping in both ruptured and unruptured aneurysms in last


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decades.[2,3] According to the study of Hwang et al., the majority of ruptured and unruptured aneurysms were coiled in US in 2002-2008.[3] However, there are considerable risks and complications such as thromboembolism, aneurysm rupture, patent artery occlusion, coil migration and vasospasm in endovascular therapy.[4] Both modalities have advantages and disadvantages which make them as complementary rather than competitive.[3] The most prominent advantage of surgical clipping is long term durability which is controversial in endovascular coiling. Long-term follow-up performed by intracranial subarachnoid aneurysm trial (ISAT) indicated that coiling had higher risk of rebleeding than clipping.[4-6] The disadvantage of surgical clipping is the fact that it requires open surgery which is accompanied with more morbidity in elderly patients.[7] Hence, durability of endovascular coiling is not a major concern in this group of patients.[6] The advantages of endovascular coiling are less invasiveness, easy access to vertebrobasilar system and multiple aneurysms in distant areas.[3] However, coiling is not useful in all aneurysms as it cannot remove intracerebral hemorrhage or mass effect of giant aneurysms.[8] In addition, the treatment modality differs significantly in ruptured and unruptured aneurysms.[9] Although there are numerous studies comparing surgical clipping and endovascular coiling, there is no study investigating outcomes of surgical clipping and endovascular coiling in our country. Our aim was to evaluate surgical clipping and endovascular coiling outcomes by comparing modified Rankin Scale (MRS) before and 1-year after procedure in both groups of patients.

## Materials and Methods

We conducted a descriptive prospective study, including 49 consecutive patients with intracranial aneurysms who underwent endovascular coiling in Imaging Medical Center of Imam Khomeini Hospital and surgical clipping in Neurosurgery Department of Shariati Hospital in Tehran, Iran from July 2011 to August 2013.

The study included all patients with intracranial aneurysms who were ruptured or unruptured. Patients with mycotic, metastatic, atherosclerotic and dissecting aneurysms, multiple aneurysm (more than 2) and giant aneurysms (more than 25 mm in size) were excluded.

An independent neurologist examined all the patients at the time of admission and followed them by phone call 1 year after intervention and scored them according to MRS. The scale runs from 0 to 6, running from perfect health without symptoms to death (0- No symptoms; 1- No significant disability. Able to carry out all usual activities, despite some symptoms; 2- Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities; 3- Moderate disability. Requires some help, but able to walk unassisted; 4- Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5- Severe disability. Requires constant nursing care and attention, bedridden, incontinent; 6- Dead.

The diagnoses were confirmed using computed tomography (CT)-scanning and/or magnetic resonance imaging (MRI) and/or angiography. Decision on treatment protocol was made based on patients' conditions and physician interest.

All the patients were examined first by neurologist or neurosurgeons and they decided if they want to refer the patient to interventional radiology department for coiling or referred to neurosurgeons for clipping.

There was a check list filled for all patients at the time of admission including demography, risk factors, MRS before and 1 year after intervention, CT scan, MRI data and procedural information.

If there were two aneurysms in opposite hemispheres, there would be a particular check list for each one. The research was concordance with ethical consideration of Tehran University of Medical Sciences.

Extracted data were analyzed with SPSS (version 16, SPSS Inc., Chicago, IL, USA). Chi-square, fisher-exact, independent-t, paired-t and Mann–Whitney U-tests were used and were considered as statistically significant at $P < 0.050$.

## Results

Twenty-seven patients underwent endovascular coiling and 21 patients underwent surgical clipping. There were 17 females (63%) in coiling group and 13 females (61.9%) in clipping group. Mean age of patients allocated to surgical treatment was 53.7 ± 13.0 and mean age of patients allocated to endovascular therapy was 51.2 ± 11.9 ($P = 0.5080$). Of 24 patients with history of hypertension, 14 patients (66.7%) were in surgical group and 10 patients (37%) were in coiling group ($P = 0.0420$). Other risk factors are featured in table 1.

**Table 1.** Comparison of risk factors among two groups

| Risk factors | Surgical Clipping [n (%)] | Interventional coiling [n (%)] | P |
|---|---|---|---|
| Hyperlipidemia | 8 (38.1) | 3 (11.1) | 0.0270 |
| Smoking | 3(14.3) | 5 (18.5) | 0.9900 |
| Cerebro vascular disease | 0 | 2 (7.4) | 0.5000 |
| Polycystic kidney disease | 0 | 1(3.7) | 0.9900 |
| Family history of Cerebrovascular diseases | 0 | 1(3.7) | 0.9900 |
| Hypertension | 14 (66.7) | 10 (37) | 0.0420 |

**Table 2.** Anatomical distribution of aneurysms

| Anterior circulation | Coiling [n (%)] | Clipping [n (%)] |
|---|---|---|
| ICA | 13 (56.6) | 1 (4.8) |
| P Com A | 1 (4.3) | 1 (4.8) |
| ACA | 0 | 3 (14.3) |
| A2 | 0 | 1 (4.8) |
| A Com A | 3 (13) | 5 (23.8) |
| MCA | 6 (26.1) | 6 (28.6) |
| AComA and MCA | 0 | 1 (4.8) |
| ACA and MCA | 0 | 2 (9.5) |
| ACA and AComA | 0 | 1 (4.8) |
| Posterior circulation | | |
| Basilar artery tip | 2 (50) | 2 (50.0) |
| Basilar artery trunk | 1 (25) | 1 (25.0) |
| Posterior cerebral artery | 1 (25) | 1 (25.0) |

ICA: Internal carotid artery; ACA: Anterior cerebral artery; MCA: Middle cerebral artery
P Com A: Posterior communicating artery; A Com A: Anterior communicating artery

Of 28 patients who presented with ruptured aneurysms at the time of admission, 17 (81%) were in the surgical group and 11 (41%) were in coiling group (P = 0.0050).

Symptoms and signs of the patients at the time of admission were hypertension in 12 (25%), vertigo in 11 (22.9%), severe headache in 27 (58.7%). Four patients (8.7%) were asymptomatic.

Forty-four (91.7%) aneurysms were located in anterior circulation, and 4 (8.3%) were in posterior circulation. The arterial distribution of aneurysms is shown in table 2.Five aneurysms (10.6%) were smaller than 4 mm, 17 (36.2%) were 4-10 mm and 25 (53.2%) were > 10 mm. The detailed distributions of the aneurysms according to their size in two groups have been mentioned in table 3. The percentage of large aneurysms was significantly higher in coiling group. Eighteen aneurysms (40.9%) had wide neck (neck diameter > 4 mm) and 26 aneurysms (59.1%) had narrow neck[8] 91.7% of aneurysms were saccular (Table 3).

The frequencies of complications during treatment among two groups have been mentioned in table 4. The frequency of focal neurologic signs was significantly higher in the clipping group.

Patients with MRS score of 1, 2 and 3 at the time of admission were 14 (29.2%) in each one. There were 4 (8.3%) persons with MRS score of 4 and 2 (4.2%) with MRS score of 5. There was no patient with MRS score of 0 in each group.

Mean MRS score at the time of admission in the endovascular group was 2.86 ± 0.974 while this figure was 3.81 ± 1.078 in the surgical group (P = 0.0040). Of 37 patients with 1 year follow-up, 19 were in the endovascular group and 18 in the surgical group. Mean MRS score of patients 1 year after procedure was 1.89 ± 0.809 and 3.67 ± 2.223 in the endovascular group and surgical group, respectively (P = 0.0100). MRS improvement is statistically significant in coiling group (P = 0.0090), but not in clipping group (P = 0.8750).

Mean difference of MRS score at the time of admission and 1 year later, was 0.947 ± 1.224 in the endovascular group and 0.111 ± 2.083 in the surgical group (P = 0.3000) (Table 5).

**Table 3.** Comparison of the anatomical properties of aneurysms between two groups

| Procedure | Neck size [n (%)] | | | Shape [n (%)] | | | | Aneurysm size [n (%)] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wide | Narrow | P | Saccular | Fusiform | Other | P | Micro | Small 4-10 mm | Large > 10 mm | P |
| Coiling | 13 (50.0) | 13 (50.0) | 0.1400 | 24 (88.9) | 2 (7.4) | 1 (3.9) | 0.9900 | 2 (7.4) | 6 (22.2) | 19 (70.4) | 0.0230 |
| Clipping | 5 (27.8) | 13 (72.2) | | 20 (95.2) | 1 (4.8) | 0 | | 3 (15.0) | 11 (55.0) | 6 (30.0) | |

**Table 4.** Complications during procedure

| Complication | Coiling [n (%)] | Clipping [n (%)] | P |
|---|---|---|---|
| Rupture | 1 (3.8) | 0 (0) | 1.0000 |
| Brain infarction | 1 (3.7) | 3 (14.3) | 0.3060 |
| Focal neurological signs | 2 (7.4) | 7 (33.3) | 0.0310 |
| Vision disturbance | 0 | 2 (10) | 0.1840 |
| Death | 0 | 1 (4.8) | 0.4470 |

**Table 5.** Mean modified Rankin Scale (MRS) scores before and at 1 year after the treatment and their difference in two groups

| Procedure | Mean MRS at the time of admission | Mean MRS at 1 year follow-up | P | Difference |
|---|---|---|---|---|
| Coiling | 2.86 ± 0.974 | 1.89 ± 0.809 | 0.0090 | 0.947 ± 1.224 |
| Clipping | 3.81 ± 1.078 | 3.67 ± 2.223 | 0.8750 | 0.111 ± 2.083 |
| P | 0.0040 | 0.0120 | | 0.3000 |

MRS: Modified Rankin scale

The distribution of different MRS scores at the time of admission and 1 year post-intervention in two groups are shown at table 6. Regarding the change of MRS in patients, there were 2 cases (10.5%) of deterioration of MRS in coiling and 7 cases (38.9%) of deterioration in clipping group. In addition, the frequency of MRS improvement was higher in coiling group, but there was not statistically significant difference between two groups (Table 7).

Hydrocephalus occurred in 4 patients at 1 year follow-up all in surgical clipping (P = 0.0350). There was no statistically difference in other complications at 1 year follow-up in two groups. (seizure seen in one patient in clipping group, infection seen in one patient in clipping group and pulmonary complication seen in one patient in the clipping group).

## Discussion

This study has been done to compare the surgical clipping with endovascular coiling in treatment of brain aneurysms in terms of risk factors, preprocedural clinical findings of the patients, anatomical properties of the aneurysms, procedural complications and 6 months follow-up disability status based on MRS.

The endovascular coiling has been introduced as the brain aneurysm treatment since 1990s and approved as a relatively minimal invasive method.[4] Few studies have focused on the comparison of the coiling and clipping in the treatment of disease.

By daily advancing in non-invasive imaging techniques such as CT and MR angiography, there are more unruptured intracranial aneurysms (UIA) incidentally detected, which management strategy remains controversial. Several studies revealed that the risk of rupture for UIAs is estimated 1% per year for aneurysms 7-10 mm in diameters.[10,11] The study of Ishibashi et al. showed that a previous history of SAH, the posterior circulation location and large size were significantly predictors of aneurysm rupture.[12] ISAT showed that endovascular coiling is the treatment of choice for ruptured intracranial aneurysms rather than neurosurgical clipping on patients suitable for either treatment, although the difference in morbidity and rate of independency decreases over time.[2,13]

In this paper, we assessed two groups of ruptured or non-ruptured brain aneurysms treated with coiling and clipping. The patients were followed up for 1 year and their disability was assessed before treatment and after this period. Our study was not randomized thus the baseline situation of the patients was not similar between two groups. Specifically, the clipping group had more ruptured aneurysms in comparison to coiling patients. This could be due to the initial situations of the patients entered the treatment facilities. Naturally, most of the patients with ruptured aneurysms referred to the hospital emergencies and then they were referred to the neurosurgery services. In this situation, they are more probable to be operated due to their emergent situation.

**Table 6.** Distribution of modified Rankin Scale (MRS) scores in two groups before and at 1 year after the treatment

| MRS score | Coiling [n (%)] | | Clipping [n (%)] | |
|---|---|---|---|---|
| | At the time of admission | At 1 year follow-up | At the time of admission | At 1 year follow-up |
| 0 | 0 | 6 (31.6) | 0 | 4 (22.2) |
| 1 | 12 (44.4) | 10 (51.6) | 2 (9.5) | 2 (11.1) |
| 2 | 8 (29.6) | 2 (10.5) | 6 (28.6) | 4 (22.2) |
| 3 | 5 (18.5) | 1 (5.3) | 9 (42.9) | 2 (11.1) |
| 4 | 2 (7.4) | 0 | 2 (9.5) | 2 (11.1) |
| 5 | 0 | 0 | 2 (9.5) | 0 |
| 6 | 0 | 0 | 0 | 4 (22.2) |

MRS: Modified Rankin Scale

**Table 7.** Trend of modified Rankin Scale (MRS) among two groups before and after the treatment

| | Coiling [n (%)] | Clipping [n (%)] | P |
|---|---|---|---|
| Deteriorated | 2 (10.5) | 7 (38.9) | |
| Unchanged | 4 (21.1) | 2 (11.1) | 0.1900 |
| Improved | 13 (68.4) | 9 (50.0) | |

MRS: Modified Rankin Scale

In addition, the patients underwent coiling had greater sized aneurysms in comparison to clipping group and the frequency of internal carotid artery aneurysms was higher than clipping group. These could be due to the fact that these aneurysms are more difficult to be operated by clipping method.

When we consider the MRS, scores in two groups, the baseline score of clipping group was worse. This could be because more patients in clipping group experienced rupture and SAH before the treatment. Worse MRS in the clipping group at the time of the procedure could be the cause of worse MRS at 1 year follow-up. Although the MRS difference of pre- and post-intervention in coiling group was greater than clipping group, this was not statistically significant between two groups.

Regarding the comparison of two treatment methods, some studies, and systematic reviews and meta-analyses have been published. These reviews are separately published on the ruptured and unruptured aneurysms. One of the most famous trials was ISAT. Up to now, multiple periodical reports have been published on the patients entered in this international follow-up trial. They have reported the comparison of the safety and efficacy of endovascular coiling versus neurosurgical clipping in patients with a ruptured intracranial saccular aneurysm. In addition, there are a few reports and systematic reviews on the unruptured brain aneurysms.

Brinjikji et al. in a study on medical records of 64,043 patients with unruptured aneurysms found coiling treatment increased from 20% in 2001 to 63% in 2008. In addition, they showed the percentage of patients discharged to long-term facilities were 14.0% (4184/29,918) in surgical clipping while it was 4.9% (1655/34,125) in coiling patients ($P < 0.0001$). In addition, patients underwent clipping had a higher mortality rate (1.2% vs. 0.6%, $P < 0.0001$). Between 2001 and 2008, the total percentage of adverse events after treatment dropped from 14.8% to 7.6%. They concluded that in unruptured aneurysms, coiling in comparison to clipping is associated with lower periprocedural morbidity and mortality in the time period of 2001-2008 in USA.[14]

Hwang et al. performed a systematic review comparing endovascular coiling versus neurosurgical clipping on patients with UIA performed according to 24 included studies (n = 31,865). Their outcome measures were glasgow outcome scale (GOS) and MRS. They showed clipping is significantly associated with higher disability based on GOS [odds ratio (OR) = 2.38; 95% confidence interval (CI) = 1.33-4.26] and MRS (OR = 2.83; 95% CI = 1.42-5.63). Comparison of complications showed worse profile for clipping in neurological and cardiac complications: 1.94 (95% CI = 1.09-3.47) and 2.51 (95% CI = 1.15-5.50), respectively. Furthermore, in clipping, short-term (≤ 6 months) disability for GOS was significantly greater (OR, 2.72; 95% CI = 1.16-6.34), but not in the long term (> 6 m) GOS (OR, 2.12; 95% CI = 0.93-4.84). They concluded that considering disability and complication in a short term, coiling is a better procedure for patients with unruptured aneurysm. However, the level of evidence for this finding is low due to the limitations of included studies; further investigations are needed for a stronger conclusion.[3]

The results of these two studies are similar to ours as the disability in our study seems to be smaller after coiling in terms of MRS. Yet, in our study, the MRS change was not different between two groups. We should consider that our patients had both ruptured and unruptured aneurysms. This makes a difference between these studies and ours as the mentioned studies only recruited unruptured aneurysms.

Li et al in a systematic review on patients with ruptured intracranial aneurysms between 1999 and 2012 included four randomized controlled trials and 23 observational studies showed according to randomized controlled trials results, coiling reduces the 1 year unfavorable outcome rate (OR = 1.48; 95% CI = 1.24-1.76), but no statistical difference in nonrandomized controlled trials (OR = 1.11; 95% CI = 0.96-1.28). Compared with patients with poor preoperative condition, good preoperative grade patients treated with coiling showed better outcomes (OR = 1.51; 95% CI = 1.24-1.84 vs. OR, 0.88; 95% CI = 0.56-1.38). Incidence of rebleeding was higher after coiling (OR = 0.43; 95% CI = 0.28-0.66), while complete occlusion rate of clipping was better (OR = 2.43; 95% CI = 1.88-–3.13). The 1 year mortality rate was similar. Vasospasm was more common after clipping whereas the ischemic infarct shunt-related hydrocephalus and procedural complication rates did not show any difference between techniques. They concluded coiling is associated with a higher risk of rebleeding, but yields a better clinical outcome especially in those patients with a good preoperative status.[15]

Hoh et al. in a study on 515 patients with aneurysmal SAH treated with coiling (n = 79), clipping (n = 413) or clipping with craniotomy for any reason (n = 23) considered vasospasm has poor outcome (according to modified Rankin score of 3-6) and in-hospital mortality. In their retrospective single center and nonrandomized study, clipping had a better outcome than coiling among good situation patients without any effect on vasospasm.[16]

Taha et al. in a retrospective study on 133 patients hold 168 aneurysm (ruptured or unruptured) showed better follow-up angiographic results in clipping (total

occlusion of 81.4% vs. 57.5%). In SAH patients, the frequency of vasospasm after angiography was 17.4% in coiling and 45.4% in clipping. In SAH patients, excellent outcome for coiling and clipping groups was seen in 62% and 44%, respectively. However, in unruptured patients, this profile was 93% vs. 81%, respectively. They concluded in ruptured and unruptured cerebral aneurysms, coiling is a safe alternative for clipping.[17]

One of the advantages of coiling is that it could be done on patients with poor condition. Weir et al. in a study on the SAH patients with Hunt and Hess grade of 4 or 5 showed despite poor medical condition and a high frequency of vasospasm during treatment these patients can undergo successful coil embolization, but morbidity and mortality are still high. These findings compare favorably with similar patients treated aggressively in surgical series.[18]

Molyneux et al. in a report of 2143 patients recruited in ISAT in Europe centers reported 1 year outcomes for 1063 patients allocated to endovascular treatment, and 1055 patients allocated to neurosurgical treatment. Among endovascular treatment patients, 250 (23·5%) were dead or dependent at 1 year, compared with 326 (30·9%) of patients underwent neurosurgery. The absolute risk reduction was 7·4% (95% CI = 3·6-11·2, P = 0·0001). The early survival advantage was maintained for up to 7 years and was significant (log-rank P = 0·0300). The risk of epilepsy was substantially lower in endovascular treated patients, while the risk of late rebleeding was higher.[19]

Renowden et al. in a study on SAH patients treated with coil embolization reported their 10-year experience. They showed failed technique in 25 patients among 717. Rupture complicated Thirty-seven procedures (4.7%) resulted in 10 permanent disability or dead (1.3%). Thromboembolic events were seen in 35 procedures (4.5%) resulting in 8 permanent disability or dead. Six procedures were complicated by dissection. Overall morbidity or mortality was 2.9%. Sixteen patients experienced another subarachnoid hemorrhage (2.3%) resulting in 12 death. At 6 months, 580 patients (82%) were independent, and 130 patients (18%) were disabled or dead. They concluded that coiling is a feasible treatment with a small mortality and permanent morbidity risk and without a high risk of rebleeding. They showed majority of patients recovered independently.[20] Our results are comparable with the results of this study.

Sturiale et al. in a systematic review on endovascular treatment in elderly patients recruited 21 studies reporting totally 1511 patients. Long-term aneurysm occlusion rate was 79% (95% CI = 70-85%). 4% experienced perioperative stroke (95% CI = 3-6%) (similar finding among ruptured and unruptured aneurysms). Rupture during procedure occurred in 1% and 4% of patients with unruptured and ruptured aneurysms, respectively. Perioperative mortality rate was greater in SAH patients (23% vs. 1%; P < 0.0100). Good clinical outcome at 1 year were 93% and 66% in patients with unruptured and ruptured aneurysms, respectively. They concluded that coiling in elder patients has a long-term occlusion rate, but regarding the morbidity and mortality in this treatment, careful patient selection is recommended especially in unruptured aneurysms.[21]

In a study done on the ISAT database for comparing recurrence of SAH, dependence and standardized mortality ratios between coiling and clipping, it was shown an increased small risk of recurrence in coiling while 5 years risk of death was significantly higher in clipping.[22]

One important point in large scale comparison of two procedures is the cost analysis. Of course, the total final cost also depends to the initial situation of the patients regarding the aneurysm rupture. The patients could be discharged to home, short term facilities, long term facilities or could be dead. These situations are associated with different costs. The greater cost has been shown in patients discharged to long term facilities.[23] In addition, the hospital stay after the procedure is very important in the total cost of procedure. This cost differs between different countries because it is related to the fundamental economic system of the country. In one study performed in the USA in 2008, it was determined costs of patients discharged to home or short term facilities was higher in patients under 65 who underwent clipping (in comparison to coiling) and this pattern was also seen in patients greater than 65 years old who discharged to home.[23] However, in the mentioned study, considering all patients, the total cost in two groups did not show statistical difference.[23] There is not any comprehensive cost analysis study in our country comparing the clipping versus coiling, but it seems regardless of physician payment, the most part of costs in clipping treatment relates to hospital stay while in coiling, it relates to the coil preparation. Hoh et al in a study of NIS in 2002-2006 found that the clipping patients experienced significantly higher hospital stay and total hospital costs than coiling among patients with ruptured aneurysms.[24]

Our study had some limitations. Patients were not good samples for comparison because of dissimilarity in ruptured aneurysms percentage, aneurysm size, aneurysm location and MRS at the time of enrollment in the study. Patients were not randomly assigned in each group and moreover, our sample size was small,

and it could lead to observed insignificant differences. Hence, the results of this research should be interpreted cautiously.

## Conclusion

There were no statistically significant differences in 1-year outcomes between two groups. We recommend further interventional studies with bigger sample sizes for better evaluation of the modalities.

## Conflict of Interests

The authors declare no conflict of interest in this study.


## Acknowledgments

We thank Professor Hamid Rahmat and Dr. Bahram Hejrani for their cooperations and guides.



**How to cite this article:** Taheri Z, Harirchian MH, Ghanaati H, Khoshnevisan A, Salamati P, Miri M, et al. Comparison of endovascular coiling and surgical clipping for the treatment of intracranial aneurysms: A prospective study. Iran J Neurol 2015; 14(1): 22-8.


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Iranian Journal of Neurology

Original Paper

Iran J Neurol 2015; 14(1): 29-34

# Accuracy of magnetic resonance spectroscopy in distinction between radiation necrosis and recurrence of brain tumors

Received: 19 Jul 2014
Accepted: 29 Nov 2014

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**Keywords**
Magnetic Resonance Spectroscopy, Tumor Recurrence, Radiation Necrosis

## Abstract

**Background:** Distinction between radiation necrosis and recurrence of intraparenchymal tumors is necessary to select the appropriate treatment, but it is often difficult based on imaging features alone. We developed an algorithm for analyzing magnetic resonance spectroscopy (MRS) findings and studied its accuracy in differentiation between radiation necrosis and tumor recurrence.

**Methods:** Thirty-three patients with a history of intraparenchymal brain tumor resection and radiotherapy, which had developed new enhancing lesion were evaluated by MRS and subsequently underwent reoperation. Lesions with Choline (Cho)/N-acetyl aspartate (NAA) > 1.8 or Cho/Lipid > 1 were considered as tumor recurrence and the remaining as radiation necrosis. Finally, pre-perative MRS diagnoses were compared with histopathological report.

**Results:** The histological diagnosis was recurrence in 25 patients and necrosis in 8 patients. Mean Cho/NAA in recurrent tumors was 2.72, but it was 1.46 in radiation necrosis ($P < 0.01$). Furthermore, Cho/Lipid was significantly higher in recurrent tumors ($P < 0.01$) with the mean of 2.78 in recurrent tumors and 0.6 in radiation necrosis. Sensitivity, specificity, and diagnostic accuracy of the algorithm for detecting tumor recurrence were 84%, 75% and 81%, respectively.

**Conclusion:** MRS is a safe and informative tool for differentiating between tumor recurrence and radiation necrosis.

## Introduction

More than half of all brain tumors are intraparenchymal.[1] Surgery is the main treatment for such tumors but microscopic spread of neoplastic cells and adjacency to eloquent areas, frequently prevents total tumor removal. Therefore, radiotherapy is necessary as an adjuvant treatment for better local control of in most patients.

A delayed complication of radiotherapy is radiation necrosis. It is a long-term complication that occurs 6 months to decades after radiation treatment. Pathologic changes include endothelial thickening of small arteries, lymphocyte and macrophage infiltration, hyalinization, fibrinoid deposition, thrombosis, and finally luminal occlusion. The vascular endothelial injuries cause damage to oligodendroglia. As a result, white matter tissue is often affected more than gray matter tissue.[2] Radiation necrosis causes symptoms such as headache, seizure, mental changes and other neurological deficits.[3] Therefore, it can mimic tumor recurrence clinically, but its management and prognosis are different.[4] Furthermore, discriminating radiation necrosis from


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recurrent intraparenchymal neoplasm by imaging can be challenging because both can have regions with avid uptake of contrast material on T1-weighted images and can cause mass effect with local edema. Therefore, it seems necessary to seek other imaging techniques to differentiate between them. In this regard, numerous studies have investigated the capabilities of new imaging techniques such as positron emission tomography (PET),[5-7] single photon emission computed tomography (SPECT),[8-10] diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS).[11,12]

MRS is a noninvasive technique, which shows metabolite profile of the brain.[13] It does not use harmful radionuclide tracers and is available in most MRI centers. Spectroscopic characteristics of radiation necrosis and recurrent tumors such as astrocytoma, oligodendroglioma and metastasis have been explained in the literature.[14-17] In this prospective study, we propose a model to analyze spectroscopic findings and investigate its accuracy in discrimination between radiation necrosis and recurrence of intraparenchymal tumors.

## Materials and Methods

Within a period of 28 months, a total of 33 patients (20 males and 13 females) with history of intraparenchymal brain tumor resection and subsequent radiotherapy (ranged from 55 to 65 Gy) were enrolled in the study. All the patients had symptoms related to a new parenchymal enhancing lesion in the vicinity of the original treated tumors. Thirteen patients had glioblastoma, six had low-grade astrocytoma, five had anaplastic astrocytoma, two had oligodenroglioma, five had metastasis and two had medulloblastoma (Table 1). All the patients were evaluated by MRS and subsequently underwent reoperation. Finally, preoperative MRS diagnoses were compared with histopathological report. After explaining the details of the procedures to the patients, Informed consent was obtained.

MRS was performed during conventional MR image acquisition with a 1.5-T MR unit, Magnetom, Vision (Siemens, Erlangen, Germany). The single-voxel technique was employed using a standard voxel volume of 8.0 $cm^3$ (2.0 × 2.0 × 2.0 cm) or at least 3.37 $cm^3$ (1.5 × 1.5 × 1.5 cm) applied in smaller lesions. The parameters utilized for acquisition were the Press technique using a TE of 144 ms. Shimming was automatically performed, followed by chemically selected saturation for water suppression. When possible, signal contamination from fat tissue in the skull and skull base was avoided. Voxels were positioned on T2-weighted images of the lesions, and adjusted spectra were always acquired before the administration of gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA). T1-weighted MR imaging with Gd-DTPA was then obtained to confirm the spatial relationship between the spectroscopic voxel and the enhanced lesion. Patients younger than 10 years of age were sedated with halothane and nitrous oxide to obtain motion-free examinations. Metabolites were always shown, on the x-axis in parts per million (ppm) and on the y-axis, by the height of the metabolite peaks in an expressed scale at an arbitrary intensity. The metabolites studied were Choline (Cho) which appears at 3.22 ppm, N-acetyl aspartate (NAA) at 2.01 ppm and lipid at 0.8-1.3 ppm. MRS data were evaluated using a commercial program (Luise; Siemens) available at the Magnetom Vision scanner. Signal intensity ratios Cho/NAA and Cho/Lipid were analyzed for the lesions. According to previous studies,[15,18] we used cut-off value of 1.8 for Cho/NAA and 1 for Cho/Lipid. Cho/NAA > 1.8 and Cho/Lipid > 1, were considered as an indicator of tumor recurrence. Also, we proposed an algorithm shown in figure 1 which uses both Cho/NAA and Cho/Lipid ratios.

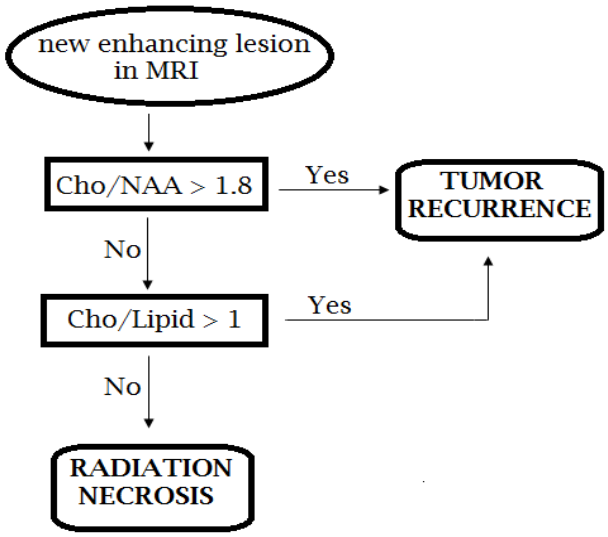


**Figure 1.** The algorithm for discrimination between tumor recurrences from radiation necrosis according to spectroscopic data
MRI: Magnetic resonance spectroscopy; Cho: Choline; NAA: N-acetyl aspartate

Preparation of biopsy specimens included neutral formalin fixation and paraffin embedding. Histological sections were stained with hematoxylin and eosin and examined with a light microscope. Tissue sections were analyzed for the presence of tumor and radiation necrosis.

## Results

Surgical resection was performed in all the 33 patients.

The histological diagnosis was recurrence in 25 patients and necrosis in 8 patients (Table 1). Typical examples of metabolic spectra obtained in a lesion consistent with radiation injury and in recurrent tumor are given in figures 2 and 3.

Mean Cho/NAA in radiation necrosis and recurrent tumors were 1.46 and 2.72 respectively, with a significant difference ($P < 0.01$). Also, Cho/Lipid was significantly higher in recurrent tumors ($P < 0.01$) with the mean of 0.6 in radiation necrosis and 2.78 in recurrent tumors.

The mean interval between completion of radiotherapy and MRS was longer in patients with radiation necrosis (16.3 months in contrast to 11.1 months), but the difference was not significant ($P = 0.07$).

MRS diagnosis using Cho/NAA value was different from diagnosis according to Cho/Lipid value, in eight patients (for example, in favor of radiation necrosis by Cho/NAA and tumor recurrence by Cho/Lipid). The final logistic regression model had an area under the receiver operating characteristic (ROC) curve of 85% using Cho/NAA and 89% using Cho/Lipid. Sensitivity, specificity, and diagnostic accuracy of Cho/NAA, Cho/Lipid and the proposed algorithm for detecting tumor recurrence, are shown in table 2.

**Table 1.** Demographic data, primary tumor pathology, total radiation dose and interval to MRS, metabolic ratios, MRS diagnosis and histopathological diagnosis of patients

| Age | Gender | Primary pathology | Radiation Dose (Gy) | Interval to MRS (months) | Cho/ NAA | Cho/ Lipid | Diagnosis a according to algorithm | Histopatholo gic diagnosis |
|---|---|---|---|---|---|---|---|---|
| 32 | F | LGA | 56 | 9 | 2.1 | 0.8 | T | T |
| 28 | M | LGA | 56 | 24 | 1.5 | 2.9 | T | T |
| 18 | F | LGA | 60 | 9 | 2.4 | 0.6 | T | T |
| 33 | M | LGA | 56 | 13 | 2.1 | 3.5 | T | T |
| 41 | M | LGA | 60 | 33 | 1.0 | 0.3 | R | R |
| 21 | F | LGA | 60 | 12 | 3.1 | 2.0 | T | R |
| 55 | M | AA | 64 | 14 | 4.2 | 3.5 | T | T |
| 41 | M | AA | 60 | 8 | 1.5 | 1.8 | T | T |
| 37 | M | AA | 64 | 22 | 3.0 | 4.7 | T | T |
| 60 | F | AA | 64 | 8 | 2.5 | 2.2 | T | T |
| 54 | F | AA | 60 | 13 | 1.1 | 0.4 | R | T |
| 68 | F | GBM | 60 | 7 | 2.5 | 2.0 | T | T |
| 44 | M | GBM | 64 | 10 | 4.7 | 5.2 | T | T |
| 38 | M | GBM | 60 | 11 | 1.6 | 0.6 | R | T |
| 55 | F | GBM | 64 | 5 | 4.7 | 3.7 | T | T |
| 64 | F | GBM | 64 | 10 | 4.1 | 6.3 | T | T |
| 41 | M | GBM | 64 | 13 | 1.5 | 0.6 | R | T |
| 57 | M | GBM | 64 | 7 | 4.1 | 4.2 | T | T |
| 71 | F | GBM | 64 | 8 | 3.9 | 2.5 | T | T |
| 63 | M | GBM | 60 | 11 | 3.1 | 0.8 | T | T |
| 51 | M | GBM | 64 | 17 | 2.0 | 0.5 | T | R |
| 54 | F | GBM | 60 | 12 | 1.5 | 0.6 | R | R |
| 39 | F | GBM | 56 | 11 | 1.3 | 0.6 | R | R |
| 35 | M | GBM | 60 | 17 | 0.8 | 0.2 | R | R |
| 51 | M | Oligo | 60 | 33 | 1.3 | 1.8 | T | T |
| 44 | M | Oligo | 64 | 20 | 1.0 | 0.4 | R | R |
| 59 | M | Met | 60 | 5 | 3.3 | 2.1 | T | T |
| 55 | F | Met | 60 | 4 | 1.8 | 4.1 | T | T |
| 66 | F | Met | 64 | 6 | 1.5 | 3.9 | T | T |
| 59 | M | Met | 60 | 7 | 1.6 | 0.8 | R | T |
| 69 | F | Met | 60 | 9 | 1.0 | 0.2 | R | R |
| 6 | F | Medulo | 54 | 14 | 3.3 | 5.4 | T | T |
| 6 | M | Medulo | 54 | 8 | 4.6 | 4.1 | T | T |

T: Denotes tumor recurrence; R: Denotes radiation necrosis; MRS: Magnetic resonance spectroscopy; Cho: Choline; NAA: N-acetyl aspartate; LGA: Low-grade astrocytoma; AA: Anaplastic astrocytoma; GBM: Glioblastoma; Oligo: Oligodenroglioma; Met: Metastasis; Medulo: Medulloblastoma

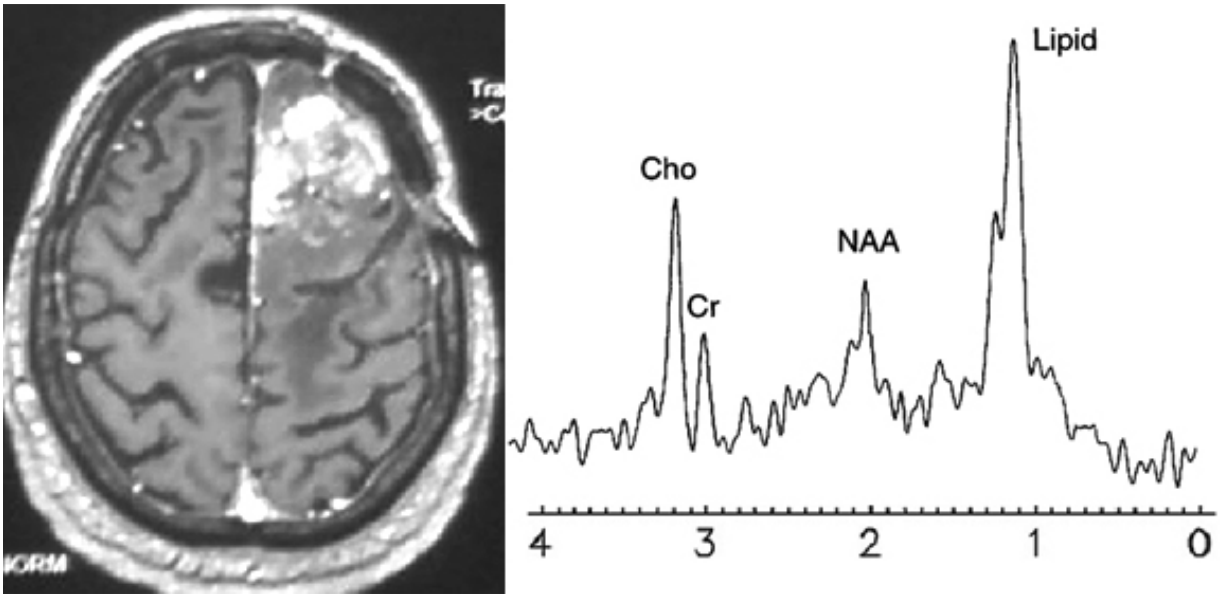


**Figure 2.** 54-year-old woman after surgical resection and radiation for left frontal glioblastoma.(case 22) (a) Axial T1-weighted image after contrast administration shows a new area of contrast enhancement in left frontal lobe. (b) Spectra showed prominent lipid peak, with slightly decreased choline (Cho)/N-acetyl aspartate ratio (1.5) and decreased Cho/lipid ratio (0.6), indicating radiation necrosis, which was confirmed at histopathology

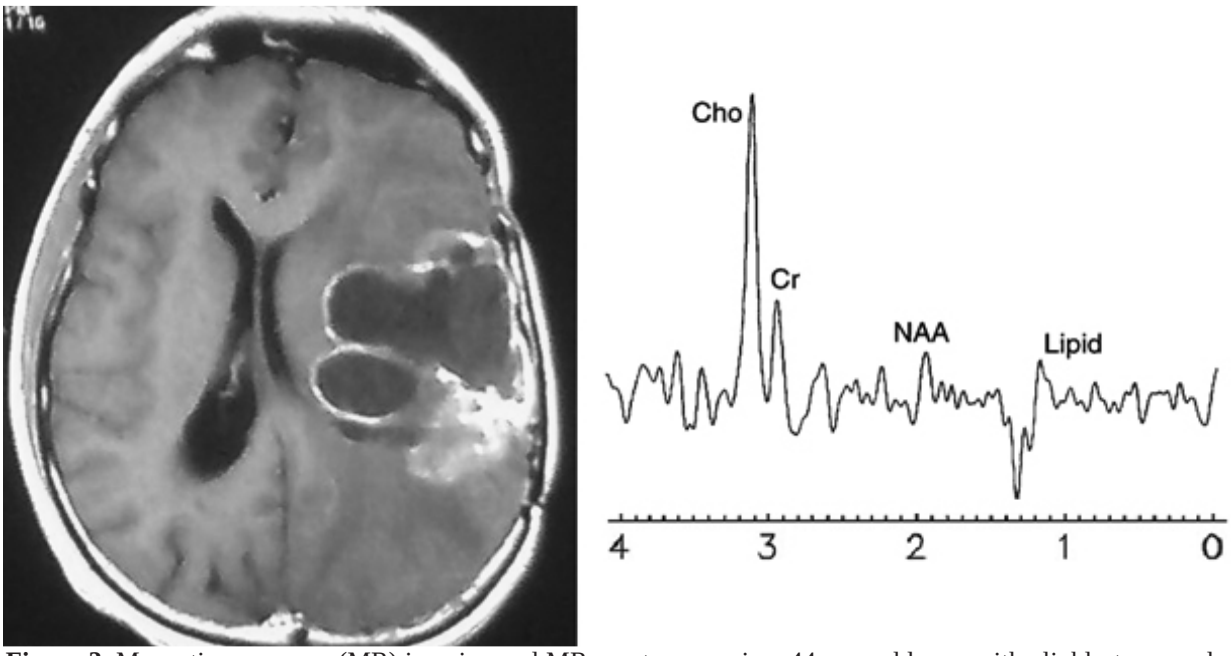


**Figure 3.** Magnetic resonance (MR) imaging and MR spectroscopy in a 44-year-old man with glioblastoma and history of surgery and radiotherapy (case 13). (a) Axial T1-weighted contrast-enhanced MR image, shows a left temporal enhancing lesion with mass effect. There is a solid enhancement in posterior part and peripheral enhancement in other areas, suggesting cyst or necrosis. (b) MR spectroscopic image, shows pathologic spectra with increased choline (Cho)/N-acetyl aspartate and Cho/lipid ratio (4.7 and 5.2, respectively), indicative of tumor recurrence. Histopathologic examination confirmed diagnosis

**Table 2.** Sensitivity, specificity and diagnostic accuracy of proposed algorithm

| Classification function | Cho/NAA (%) | Cho/Lipid (%) | Algorithm (%) |
|---|---|---|---|
| Sensitivity | 73 | 87 | 84 |
| Specificity | 75 | 87 | 75 |
| Diagnostic accuracy | 69 | 75 | 81 |

Cho: Choline; NAA: N-acetyl aspartate

## Discussion

In patients with intraparenchymal brain tumors and history of surgery and radiotherapy, it is important to differentiate between radiation necrosis and tumor recurrence to choose appropriate treatment and predict prognosis. In both situations, conventional MRI usually shows enhancing lesion with or without mass effect, so it cannot be conclusive. New imaging techniques such as PET, SPECT, DWI and MRS have been studied extensively to analyze their capabilities in discriminating between radiation necrosis and tumor recurrence. MRS is an inexpensive imaging technique that does not use harmful radionuclide tracers and can be performed with conventional MRI at the same time. There are many studies in the literature explaining spectroscopic characteristics of radiation necrosis and tumor recurrence.

Spectroscopic changes in radiation necrosis include slight depression of NAA and variable changes in Cho and Cr. Also, it may show Lipid or Lactate peak reflecting cellular debris in the lesion.[15] In contrast, recurrent neoplastic lesions show prominent elevation of Cho peak due to high turnover of cell membrane.[13,19-23] In order to reliable distinction of tumor recurrence and radiation necrosis according to spectroscopic findings, different metabolites and their ratios have been studied and some cutoff values have been introduced.

Kimura et al. used Cho/Lip or Lac ratio and found that in cases of radiation necrosis, a high lipid-dominant peak was observed from the central non-enhanced region, along with a low Cho peak and a low NAA peak.[24] Similar figures were found in another study by the same group in which the authors could differentiate ring-enhancing lesions as "space-occupying radiation necrosis" from ring-enhancing metastasis in all 6 cases by using MRS.[25]

Using multi-voxel MRS, Rock et al. claimed that a Cho/Cr ratio > 1.79 or a lipid and Lactate/Cho ratio < 0.75 has sevenfold increased odds of being pure tumor compared with pure necrosis.[26] Weybright et al. reported that when cutoff values of 1.8 for either Cho/NAA or Cho/Cr were used, 27 of 28 patients (97%) were retrospectively correctly diagnosed.[18] In another study using multi-voxel 3D MRS, the investigators found the Cho/NAA and Cho/Cr ratios to be significantly higher in recurrent tumor than in radiation injury, whereas the NAA/Cr ratios were lower in recurrent tumor than in radiation injury. When they used ROC analysis, the resulting sensitivity, specificity, and diagnostic accuracy of 3D MRS were 94.1%, 100%, and 96.2%, respectively, based on the cut-off values of 1.71 for Cho/Cr or 1.71 for Cho/NAA or both as tumor criteria.[27] Smith et al. studied 33 patients retrospectively and concluded that an elevated Cho/NAA ratio correlated with evidence of tumor recurrence.[28]

In our study, Cho/NAA and Cho/Lipid were significantly different between tumor recurrence and radiation necrosis. According to previous studies, we used cut-off value of 1.8 for Cho/NAA and 1 for Cho/Lipid (Figures 2 and 3). Both ratios had an acceptable accuracy but combining them by using algorithm shown in figure 1 resulted in greater diagnostic accuracy than each ratio (Table 2). Area under the ROC curve was 85% for Cho/NAA and 89% for Cho/Lipid which showed excellent discrimination between tumor recurrence and radiation necrosis.

There were 6 patients with wrong MRS diagnosis. In three patients with neoplastic lesion, spectroscopic diagnosis was radiation necrosis; and in two of them, the lesions had a large volume (> 50 $cm^3$) and it is probable that the neoplastic portion of the lesion was not included in MRS voxel. Therefore, it seems necessary to examine all portions of large lesions.

The mean interval between completion of treatment and MRS was calculated in the two groups and it was 11.1 months in recurrent tumors and 16.3 months in radiation necrosis. Although the difference was not significant (P = 0.07), it may indicate that radiation necrosis is a long-term complication and it is uncommon in early stages, especially in 6 months after radiation therapy.

We believe that MRS has an acceptable accuracy in patients with an enhancing brain lesion and history of intraparenchymal tumor resection and radiation. Considering the noninvasiveness and availability of MRS, it is reasonable to perform MRS in these patients. Addition of other imaging techniques (such as DWI) to spectroscopic data may improve the accuracy.

## Conclusion

In patients with intraparenchymal brain tumor and history of tumor resection and radiation who have developed new enhancing lesion, MRS is a safe and informative tool for differentiating between tumor recurrence and radiation necrosis. It is necessary to examine different portions of the high volume lesions.

## Conflict of Interests

The authors declare no conflict of interest in this study.


## Acknowledgments

We would like to express our gratitude to all patients and their families, and the staff of the Neurosurgery Ward of Shariati Hospital.

**How to cite this article:** Anbarloui MR, Ghodsi SM, Khoshnevisan A, Khadivi M, Abdollahzadeh S, Aoude A, et al. Accuracy of magnetic resonance spectroscopy in distinction between radiation necrosis and recurrence of brain tumors. Iran J Neurol 2015; 14(1): 29-34.

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Iranian Journal of Neurology

Original Paper

Iran J Neurol 2015; 14(1): 35-40

# Elevated troponin T after acute ischemic stroke: Association with severity and location of infarction

Received: 18 Jun 2014
Accepted: 31 Aug 2014

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**Keywords**
Troponin, Stroke, Location, National Institutes of Health Stroke Scale, Electrocardiography, Creatinine

## Abstract

**Background:** Serum troponin elevation, characteristic of ischemic myocardial injury, has been observed in some acute ischemic stroke (AIS) patients. Its cause and significance are still controversial. The purpose of this study is to find determinants of troponin elevation and its relationship with stroke severity and location.

**Methods:** Between January 2013 and August 2013, 114 consecutive AIS patients confirmed by diffusion-weighted magnetic resonance imaging were recruited in this study. Serum troponin T level was measured as part of routine laboratory testing on admission. Ten lead standard electrocardiogram (ECG) was performed and stoke severity was assessed based on National Institutes of Health Stroke Scale (NIHSS).

**Results:** Troponin T was elevated in 20 (17.6%) of 114 patients. Patients with elevated troponin were more likely to have higher age, higher serum creatinine and ischemic ECG changes. Troponin levels were higher in patients with more severe stroke measured by NIHSS [7.96 (6.49-9.78) vs. 13.59 (10.28-18.00)]. There was no association between troponin and locations of stroke and atrial fibrillation. There were 6 (5%) patients with elevated troponin in the presence of normal creatinine and ECG.

**Conclusion:** Stroke severity, not its location, was associated with higher troponin levels. Abnormal troponin levels are more likely, but not exclusively, to be due to cardiac and renal causes than cerebral ones.

## Introduction

Troponin is a sensitive marker of myocardial injury.[1] Rise in serum troponin is characteristic for myocardial ischemic injury; however it can rise in several other conditions (e.g. renal failure, heart failure, pulmonary edema, and sepsis).[2,3] In the last decade, much interest has been drawn to the importance of serum troponin level in acute stroke. Previous studies have shown that troponin is elevated in 10-30% of acute stroke patients.[4-6] This rise can be due to concomitant coronary artery disease and myocardial infarction (MI), congestive heart failure, renal insufficiency or direct neurogenic myocardial injury.[7,8] Some researchers have found association between troponin level and location and size of infarction, severity of stroke [measured by National Institutes of Health Stroke Scale (NIHSS)], ischemic electrocardiogram (ECG) changes and increased mortality.[9-12] The purpose of this study is to investigate the relationship between cardiac troponin T and severity and location of a stroke.

## Materials and Methods

Subjects with a diagnosis of acute ischemic stroke (AIS) presenting to Shariati Hospital Tehran, Iran from January 2013 to August 2013 were enrolled. Stroke patients were diagnosed according to World Health Organization definition (sudden neurological deficit that has a presumable vascular etiology) and were diagnosed as AIS if their brain computed tomography (CT) scan was normal or showed acute ischemic changes. Ischemic stroke was confirmed by showing diffusion restriction on diffusion-weighted


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imaging magnetic resonance imaging (MRI) using Siemens Magnetom Avanto 1.5 Tesla (Siemens Medical Solutions, Erlangen, Germany). When MRI could not be performed (e.g. cardiac pacemaker), acute stroke was confirmed by showing new hypodensity on repeat brain CT scan 4 days later. Stoke severity was assessed based on NIHSS.

Serum troponin T was measured as part of routine laboratory testing on admission. Levels of Troponin T were measured by Elecsys and cobas e analyzer (Roche diagnostics) and was considered abnormal if it was ≥ 24 ng/l. Ten lead standard ECG was performed and repeated every hour if there was any sign of ischemic changes (i.e., ST-T changes and Left Bundle Branch Block).

Descriptive statistics was shown as mean. P-P plot (which plots a variable cumulative proportion against cumulative proportions of a normal distribution, if the selected variable follows a normal distribution, points cluster around a straight line) and Kolmogorov–Smirnov test were used to assess normal distribution violation of variables. T-test and Kruskal–Wallis test, when non-parametric test had to be used, were used to compare groups in their troponin levels. Spearman correlation coefficient was used to assess the correlation between NIHSS and troponin level. Univariate general linear model was used to control for confounding variables in assessment of the association between stroke severity and troponin level. $P < 0.500$ was considered as significant. All analyses were done using SPSS software (version 21, SPSS Inc., Chicago, IL, USA).

## Results

A total of 120 AIS patients were enrolled. After review of patients' records, 6 of them were excluded because their troponin levels were not measured. Compared with included patients, they were non-significantly younger (59.67 ± 17.33 vs. 66.34 ± 14.98), more masculine (83.3 vs. 55.3%), and had non-significant less severe strokes (6.17 ± 5.04 vs. 8.18 ± 6.59).

Table 1 shows patients' basic characteristics. The precise location of a stroke could not be determined in 9 (7.9%) patients because MRI could not be done and repeated CT was inconclusive. Mean time of onset to admission was 23.76 ± 31.01 h. If 6 patients who were admitted more than three days after onset of symptoms were excluded, mean time of onset to admission would be 17.75 ± 17.85.

Table 2 shows ECG changes seen among patients. ECG ischemic changes were seen in 20% of patients.

Table 3 shows brain areas that were affected by infarcts. About two-third of strokes occurred in posterior circulation.

**Table 1.** Basic characteristics of enrolled acute ischemic stroke (AIS) patients

| Basic characteristic | Value |
|---|---|
| Age (mean ± SD) | 66.34 ± 14.98 |
| Female sex [n (%)] | 51 (44.7) |
| Time from onset (Hour) [n (%)] | |
| < 5 | 17 (14.9) |
| 5-12 | 39 (34.2) |
| 13-24 | 24 (21.1) |
| 25-48 | 11 (9.6) |
| 49-72 | 5 (4.4) |
| ≥ 73 | 6 (5.3) |
| Unknown | 12 (10.5) |
| NIHSS [n (%)] | |
| 0-9 | 74 (64.9) |
| 10-19 | 31 (27.2) |
| 20-42 | 9 (7.9) |
| Use of rTPA [n (%)] | 5 (4.4) |
| Abnormal serum creatinine [n (%)] | 9 (7.9) |
| Serum troponin (ng/l) | |
| Minimum | 1 |
| Maximum | 356 |
| Mean ± SD | 22.61 ± 43.63 |
| Median | 11.75 |
| Abnormal [n (%)] | 20 (17.5) |

NIHSS: National Institutes of Health Stroke Scale, rTPA: Recombinant tissue plasminogen activator

**Table 2.** Electrocardiogram (ECG) changes of enrolled acute ischemic stroke (AIS) patients

| ECG changes | n (%) |
|---|---|
| ST elevation | 3 (2.5) |
| ST depression | 6(5.0) |
| T inversion | 16(14.2) |
| ST-T changes | 20(16.7) |
| Atrial fibrillation | 15(12.5) |
| Dynamic ECG changes | 3(2.5) |
| LBBB | 5(4.2) |
| RBBB | 3(2.5) |
| Ischemic changes (ST-T, LBBB) | 25(21.9) |

ECG: Electrocardiogram; LBBB: Left bundle branch block; RBBB: Right bundle branch block

**Table 3.** Infarct locations of enrolled acute ischemic stroke (AIS) patients

| Location of stroke | n (%) |
|---|---|
| Right hemisphere | 59 (56.2) |
| Left hemisphere | 52 (49.5) |
| Brainstem | 21 (20.0) |
| Cerebellum | 13 (12.4) |
| Frontal | 52 (49.5) |
| Parietal | 32 (30.5) |
| Temporal | 8 (7.6) |
| Occipital | 7 (6.7) |
| Insula | 24 (22.9) |
| Basal ganglia | 21 (20.0) |
| Internal capsule | 13 (12.4) |
| Thalamus | 5 (4.8) |
| Lacunar | 22 (21.0) |
| Cortical | 51 (48.6) |

Mean of serum troponin was 22.61 ± 43.63. It was abnormal in 20 (17.5%) patients. Figure 1 shows that serum troponin level did not have a normal distribution (P < 0.001). After logarithmic transformation it had a normal distribution (P = 0.260), and was used in the transformed shape in further analyses.

Table 4 shows association of different variables with serum troponin levels in bivariate analyses. Serum troponin was significantly higher among older, male, uremic stroke patients, or patients who had ischemic changes in their ECGs.

Although dichotomizing NIHSS did not yield significant association between this variable and serum troponin, figure 2 shows that there was a weak linear association between NIHSS and serum troponin (spearman correlation coefficient = 0.20; P = 0.030). Among other stroke variables, only cerebellum strokes were significantly associated with serum troponin.

Four stroke variables which had P < 0.200 in univariate analyses were entered in a multivariate analysis after exclusion of subjects who had either abnormal creatinine levels or ischemic ECG changes. Only NIHSS remained a significant predictor of troponin levels. After adjustment by age and sex, NIHSS was still a significant predictor (P = 0.002). However, the effect of NIHSS on troponin level was too small in a way that mean of troponin among stroke patients with NIHSS < 10 was 7.96 [95% confidence interval (CI) = 6.49-9.78] compared with 13.59 (95% CI = 10.28-18.00) in patients with NIHSS ≥ 10. And, among subjects with ECG ischemic signs, NIHSS was not a significant predictor of troponin (71.55 ± 112.05 vs. 29.88 ± 29.35 in subjects with NIHSS 0-9 vs. 10-42, respectively).

There were 78 AIS subjects without any evidence of renal impairment or ECG ischemic signs. 8 of them (10%) had abnormal troponin levels; 6 of them were older than 70 and 4 had NIHSS more than 9. All 8 subjects had at least one of these predictors.

## Discussion

Stroke is the second-fourth most common cause of death, after ischemic heart disease (IHD);[13] meanwhile, IHD is the second most common cause of death after stroke.[14,15] While stroke and IHD share the same risk factors (i.e., hypertension, hyperlipidemia, diabetes mellitus and smoking), it is not unexpected to see both diseases in one patient.[16] Many studies have shown elevated serum troponin in significant proportion of acute stroke patients (11-36.4%).[4,17-19]

17.5% of acute stroke patients in our study had elevated serum troponin level which was congruent with previous studies. Associations, causes and value of troponin rise have been the core of many studies. It has been demonstrated that troponin elevation could be associated with higher age, more severe stroke, larger stroke, specific stroke locations, renal dysfunction, previous IHD, ECG changes and poor outcome.[20-23] In our study, this association was found just between troponin T and age, renal impairment, ECG changes and stroke severity (i.e. NIHSS).

We did not measure infarction size, and outcome determination was not in design of our study. Renal impairment and ischemic ECG changes were greater determinant than NIHSS; in a way that in patients with high creatinine or ischemic ECG changes, effect of NIHSS on troponin was not significant. However in patients without ischemic ECG or renal problem, higher troponin was seen in patients with more severe stroke. This effect was independent and could not be explained by other factors.

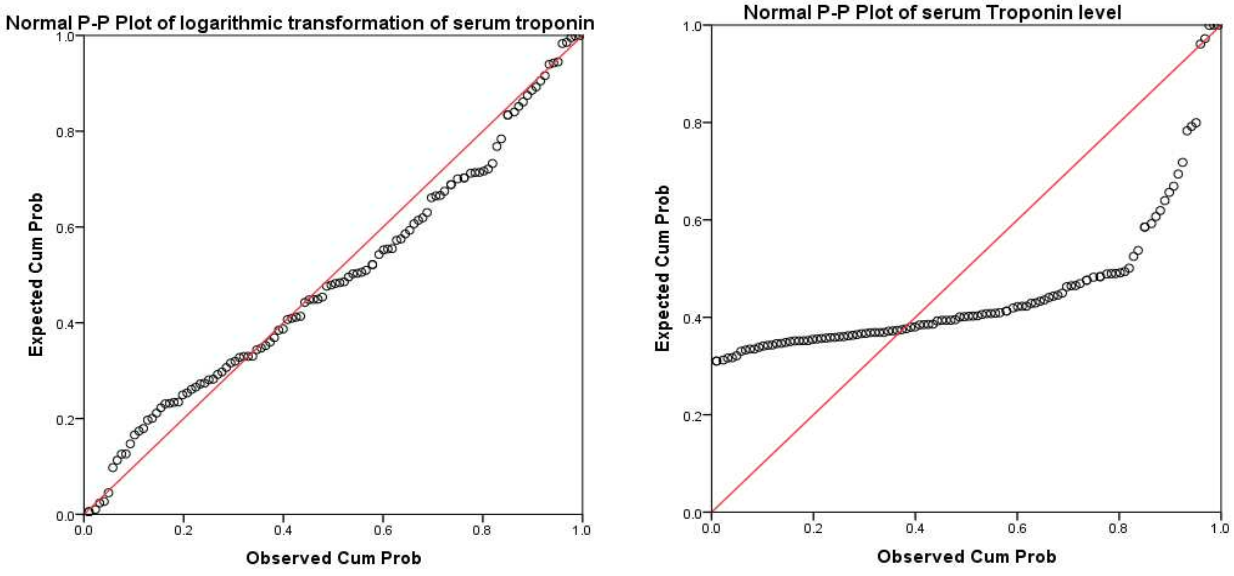


**Figure 1.** P-P plot of serum troponin level and its logarithmic transformation

**Table 4.** Association of different variables with serum troponin levels among acute ischemic stroke (AIS) patients

| Variable | Troponin (ng/l) | Logarithm of troponin | P (on logarithm of troponin) |
|---|---|---|---|
| Sex | | | |
| Male | 29.44 ± 56.10 | 2.73 ± 0.99 | 0.008 |
| Female | 14.18 ± 16.44 | 2.24 ± 0.92 | |
| Age | | | |
| < 70 | 22.56 ± 56.70 | 2.23 ± 1.08 | 0.002 |
| ≥ 70 | 22.67 ± 25.03 | 2.79 ± 0.80 | |
| Serum creatinine (mg/dl) | | | |
| ≤ 1.5 | 20.25 ± 42.78 | 2.43 ± 0.94 | 0.001 |
| > 1.5 | 52.51 ± 49.39 | 3.56 ± 1.00 | |
| Ischemic changes | | | |
| No | 14.63 ± 15.00 | 2.32 ± 0.86 | < 0.001 |
| Yes | 53.43 ± 87.44 | 3.16 ± 1.20 | |
| NIHSS | | | |
| 0-9 | 24.08 ± 52.52 | 2.41 ± 1.08 | 0.140 |
| 10-42 | 19.90 ± 18.46 | 2.70 ± 0.76 | |
| Right hemisphere | | | |
| No | 17.00 ± 17.04 | 2.49 ± 0.86 | 0.760 |
| Yes | 25.96 ± 57.75 | 2.44 ± 1.09 | |
| Left hemisphere | | | |
| No | 23.84 ± 57.75 | 2.35 ± 1.06 | 0.250 |
| Yes | 20.20 ± 26.12 | 2.57 ± 0.91 | |
| Brainstem | | | |
| No | 22.43 ± 47.17 | 2.48 ± 0.99 | 0.750 |
| Yes | 20.47 ± 34.53 | 2.40 ± 1.02 | |
| Cerebellum | | | |
| No | 14.41 ± 14.78 | 2.34 ± 0.82 | 0.045 |
| Yes | 76.00 ± 110.10 | 3.33 ± 1.58 | |
| Insula | | | |
| No | 21.44 ± 47.41 | 2.40 ± 1.00 | 0.240 |
| Yes | 24.05 ± 35.26 | 2.67 ± 0.93 | |
| Frontal | | | |
| No | 25.57 ± 57.65 | 2.50 ± 1.00 | 0.690 |
| Yes | 18.44 ± 25.98 | 2.42 ± 0.99 | |
| Parietal | | | |
| No | 23.50 ± 50.52 | 2.44 ± 1.06 | 0.740 |
| Yes | 18.71 ± 28.00 | 2.51 ± 0.80 | |
| Occipital | | | |
| No | 22.77 ± 46.19 | 2.48 ± 1.00 | 0.410 |
| Yes | 11.85 ± 12.03 | 2.16 ± 0.80 | |
| Temporal | | | |
| No | 22.52 ± 46.49 | 2.45 ± 1.01 | 0.660 |
| Yes | 16.18 ± 10.47 | 2.61 ± 0.63 | |
| Thalamus | | | |
| No | 22.78 ± 45.76 | 2.50 ± 0.98 | 0.080 |
| Yes | 7.20 ± 4.31 | 1.70 ± 1.00 | |
| Basal ganglia | | | |
| No | 20.62 ± 46.38 | 2.39 ± 0.97 | 0.150 |
| Yes | 27.75 ± 38.18 | 2.74 ± 1.04 | |
| Internal capsule | | | |
| No | 23.49 ± 47.55 | 2.49 ± 1.03 | 0.390 |
| Yes | 11.77 ± 10.17 | 2.24 ± 0.65 | |
| Cortical | | | |
| No | 25.57 ± 57.16 | 2.46 ± 1.10 | 0.980 |
| Yes | 18.30 ± 26.09 | 2.46 ± 0.87 | |

NIHSS: National Institute of Health Stroke Scale

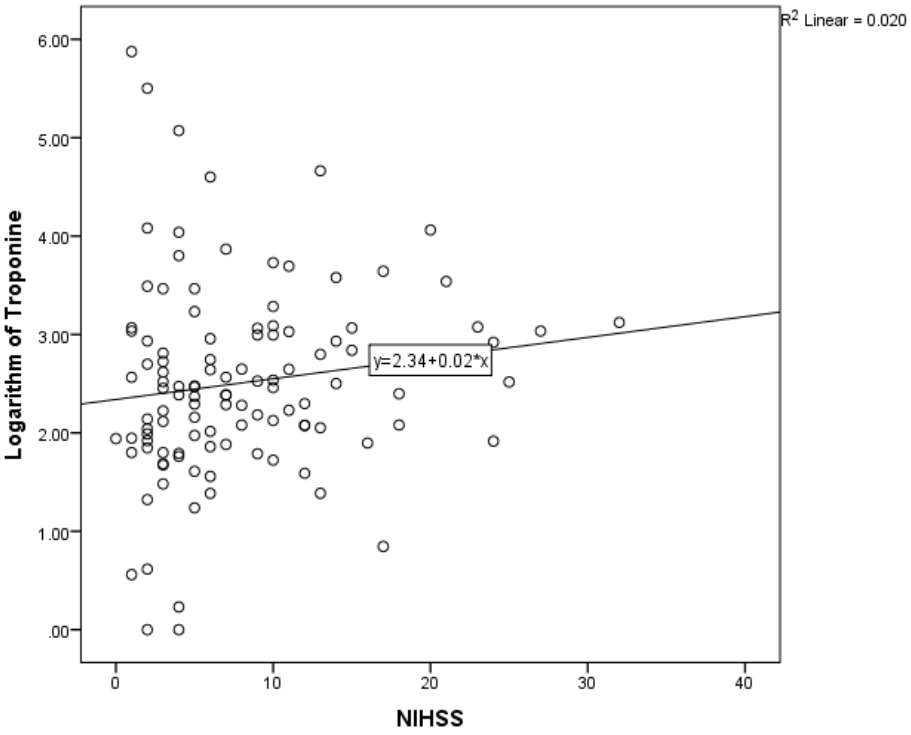


**Figure 2.** Association between National Institute of Health Stroke Scale (NIHSS) and serum troponin level among acute ischemic stroke patients

It has been hypothesized that damage to centers regulating autonomic function can cause autonomic dysregulation resulting in sympathetic overflow and neurogenic myocardial injury.[24] Therefore, insula and brainstem were center of attention of many researchers.[25] Some studies have shown that troponin level is higher in the right insular, brainstem or middle cerebral artery territory infarction.[5,10,26,27] Nevertheless, our findings along with the study of Barber and Morton. did not corroborate those results, and we found no correlation between stroke location and troponin level.[28]

Apart from associations of it, the possible causes of troponin elevation in AIS have been investigated previously. Jensen et al.[7] and Scheitz et al.[29] proposed that the most likely causes of increased troponin in AIS patients are silent acute MI before stroke, heart failure and renal insufficiency. Our data also show that most troponin elevations in AIS patients occurred in the context of renal or cardiac dysfunction and 3 (2.5%) of the patients had concomitant acute MI. However, there were 8 patients with elevated troponin (mean 43.75) at the presence of normal ECG and renal function. In these patients, troponin elevation could not be attributed to renal or cardiac problem, and neurogenic cardiac injury could be suspected. Nonetheless, we did not go through those cases and coronary status was not evaluated to be sure of the absence of coronary artery disease as predisposing factor for troponin elevation.

According to our findings, although there are some AIS patients with possible neurogenic myocardial injury, it is prudent to be vigilant in those with high troponin and perform appropriate cardiac and renal evaluation.

This was the first Troponin-Stroke relationship study in Iranian population. The number of patients (sample volume) was limited to 114, which made specific location stroke groups small, and might have made probable associations statistically insignificant. As mentioned, we did not evaluate cardiac structural (echocardiography) and coronary status; therefore the number of real neurogenic myocardial injury patients might have been over- or underestimated.

## Conclusion

Troponin T elevation in AIS patients was associated with higher age, creatinine, ECG changes and severity of stroke, but location of stroke was not a determinant factor. Cardiac and renal impairment were the cause of troponin elevation in the majority of patients; however, there are some patients with possible neurogenic myocardial injury.

## Conflict of Interests

The authors declare no conflict of interest in this study.

## Acknowledgments

We acknowledge all residents of the Neurology Ward of Shariati Hospital who participated in this study.

**How to cite this article:** Abdi S, Oveis Gharan Sh, Sinaei F, Ghorbani A. Elevated troponin T after acute ischemic stroke: Association with severity and location of infarction. Iran J Neurol 2015; 14(1): 35-40.

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Iranian Journal of Neurology

Original Paper

Iran J Neurol 2015; 14(1): 41-46

# Proposed equation between flexor carpi radialis H-reflex latency and upper limb length

Received: 03 Sep 2014
Accepted: 12 Dec 2014

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**Keywords**
H-reflex, Normal Volunteers, Arm

**Abstract**

**Background:** H-reflex is a valuable electrophysiological technique for assessing nerve conduction through entire length of afferent and efferent pathways, especially nerve roots and proximal segments of peripheral nerves. The aim of this study was to investigate the relation between normal values of flexor carpi radialis (FCR) H-reflex latency, upper limb length and age in normal subjects, and to determine whether there is any regression equation between them.

**Methods:** By considering the criteria of inclusion and exclusion, 120 upper limbs of 69 normal volunteers (68 hands of 39 men and 52 hands of 30 women) with the mean age of 39.8 ± 11.2 years participated in this study. FCR H-reflex was obtained by standard electrodiagnostic techniques, and its onset latency was recorded. Upper limb length and arm length were measured in defined position. The degree of association between these variables was determined with Pearson correlation and linear regression was used for obtaining the proposed relations.

**Results:** Mean FCR H-reflex latency was found to be 15.88 ± 1.27 ms. There was a direct linear correlation between FCR H-reflex latency and upper limb length (r = 0.647) and also arm length (r = 0.574), but there was no significant correlation between age and FCR H-reflex latency (P = 0.260). Finally, based on our findings, we tried to formulate these relations by statistical methods.

**Conclusion:** We found that upper limb length and arm length are good predictive values for estimation of normal FCR H-reflex latency but age, in the range of 20-60 years old, has no correlation with its latency. This estimation could have practical indications in pathologic conditions.

## Introduction

One type of electrophysiological late responses was described by Hoffmann, hence it is named as H-reflex.[1] This reflex is an electrical analog of the monosynaptic stretch reflex provoked by bypassing the muscle spindle and is obtained in only a few muscles in normal adults and can be elicited by submaximal stimulation of the nerves.[2,3] The stimulus travels along the Ia fibers and through the dorsal root ganglion, then it is spread to the anterior horn cell, which fires it down along the alpha motor axon to the muscle. It can be simply attained in soleus muscle (with stimulation of posterior tibial nerve at popliteal fossa), flexor carpi radialis (FCR) muscle (with stimulation of median nerve at elbow), and quadriceps muscle (with femoral nerve stimulation).[4]

H-reflex is a valuable electrodiagnostic technique for assessing nerve conduction through entire length of afferent and efferent pathways, especially at proximal segment of peripheral nerve, and also for evaluating neurophysiological changes in compromised nerve roots and efficacy of some of



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nonsurgical managements on patients with radiculopathy.[5-7] While studying H-reflex in clinical situations such as evaluation of patients suspected to radiculopathies, electromyographers usually use the parameter of latency for their interpretations and its amplitude less likely get attention because of wide variability. H-reflex is usually present in normal subjects, but this is not permanently correct. Symmetrically absent H-reflexes are not essentially abnormal and percentage of absent responses increases inelderly.[8] The most common parameter of H-reflex used, is prolonged onset latency and/or absence of H-reflex on affected side.[9-15]

Many studies have found that H-reflex of lower limbs is strongly correlated with both age and leg length. Ghavanini et al. studied the role of various constitutional factors influencing H-reflex latency and among them limb length was the only variable strongly correlated with H-reflex latency.[16] A nomogram and regression equation for obtaining individual optimal soleus H-reflex latencies have been represented by Braddom and Johnson.[17,18]

Regarding H-reflex in upper limbs there are very limited studies published in literature.[5,12-14] To the best of our knowledge, there are only two published articles by Schimsheimer et al.[12] and Schimsheimer et al.[13], which have introduced equations for estimation of optimal FCR H-reflex latency but these equations have not get popularity due to their complexity.

According to importance of FCR H-reflex latency in diagnosis of C6-C7 radiculopathies and limited studies in this field, we decided to perform a study in order to investigate relation between FCR H-reflex latency, upper limb length, arm length-a parameter of proximal upper limb length that has not been considered in previous studies-and age in normal Iranian population. In addition, we tried to find a practical formula for calculating and estimating optimal FCR H-reflex latency based on these parameters.

## Materials and Methods

This cross-sectional study was carried out from October 2013 to April 2014 among 120 upper limbs of healthy volunteers with an age range of 20-60 years. Samples were selected with a conventional method from volunteers and patients referred to academic electrodiagnostic centers, after explaining the procedure and taking written consent.

All of the participants were persons who had neither signs nor symptoms of neurologic abnormalities of upper extremities in their history and physical examination. The subjects who had any history of hereditary polyneuropathies (e.g., Charcot-Marie-Tooth), acquired polyneuropathies (e.g., diabetic polyneuropathy), any scar formation or history of fracture in their upper limbs, including the sites of stimulation or recording were excluded from our research.

The procedure was done in a setting with mean room temperature of 25 °C and skin temperature of 32-34 °C while the subject lying supine.[19] All electrodiagnostic tests were performed with Cadwell Sierra Wave electromyography machine. Surface stimulating bar electrode with 0.5 cm in diameter and cathode-anode distance of 2 cm was applied longitudinally on median nerve in antecubital fossa with cathode proximal to anode. Surface E-1 recording electrode was positioned over belly of FCR muscle located one third of distance between medial epicondyle and radial styloid and an E-2 recording electrode was placed over brachioradialis muscle. As a ground, a metal electrode was applied on skin of forearm just proximal to E-1 electrode (Figure 1).

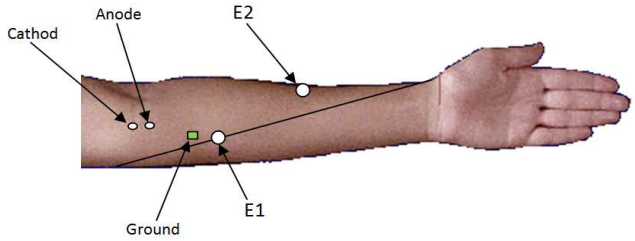


**Figure 1.** The placement of electrodes in recording of flexor carpi radialis (FCR) H-reflex

The electrodes were not removed until the whole experiment was completed to ensure exact placement and consistent results.[20] A pulse width of 0.5-1 ms was delivered at a frequency of one pulse per 2-3 s to median nerve. Sweep speed of instrument was 5 ms/div with sensitivity between 0.5 and 1 mV/div. Onset latency of H-reflex was measured from stimulus artifact to the first deflection from baseline. Stimulating electrode placement was considered acceptable when maximum H-reflex could be elicited with minimal or no M response and presence of H-reflex verified by increasing the stimulus intensity and observing a disappearance of the response and replacement by an F-wave. At least five H-responses were studied for analysis to ensure its reproducibility.

Upper limb length was measured in centimeters from C6 spinous process to tip of the third digit while arm was in 90°abduction, elbow in full extension, forearm in pronation and digits in the extension. Arm length was also measured in the same position from C6 spinous process to tip of olecranon.

Data analysis was performed by SPSS for Windows (version 16, SPSS Inc., Chicago, IL, USA). $P < 0.050$ accepted as statistically significant. Results are presented as means ± standard deviation. Independent T-test was used for analyzing sex-related differences and degree of

association between variables was determined with Pearson correlation. Linear regression was used for obtaining proposed relations.

## Results

Based on inclusion and exclusion criteria, 120 upper limbs of 69 healthy subjects (68 hands of 39 men and 52 hands of 30 women) participated in this study. The study was performed on both hands of 51 subjects but it was carried out in one hand of each of other 18 participants because of different problems (10 had symptoms of paresthesia, 5 had positive Tinel or Compression signs and 3 had scar formation on their other hand).

The subjects' mean upper limb length was 88.5 ± 3.6 cm with a range of 81.3-95.7 cm and mean arm length were 45.8 ± 2.3 cm with a range of 41.3-50.3 cm. Mean FCR H-reflex latency was 15.88 ± 1.27 ms with a range of 13.34-18.42 ms.

Independent T-test analysis revealed statistically significant differences between men and women in FCR H-reflex latency, upper limb length and arm length which are shown in table 1.

Pearson correlation shows that there is a direct linear correlation between upper limb length and FCR H-reflex latency($r = 0.647$, $P < 0.001$) and also between arm length and FCR H-reflex latency ($r = 0.574$, $P < 0.001$), but there was no significant correlation between age and FCR H-reflex latency ($P = 0.260$). All correlation coefficients are shown in table 2. The regression XY chart depicted in figures 2 and 3.

Based on linear regression analysis the following formulae for the prediction of optimal FCR H-reflex latency were obtained:

FCR H-reflex latency (ms) = 0.23 × upper limb length (cm) –4.3

FCR H-reflex latency (ms) =0.32 × arm length (cm) + 1.1.

**Table 1.** Independent T-test analysis for difference of variable means among men and women

| Variable | Mean ± SD | | P |
|---|---|---|---|
| | Men | Women | |
| FCR H-reflex latency (ms) | 16.3 ± 1.2 | 15.4 ± 1.2 | < 0.001 |
| Upper limb length (cm) | 90.4 ± 3.1 | 86.0 ± 2.6 | < 0.001 |
| Arm length (cm) | 47.0 ± 2.0 | 44.3 ± 1.6 | < 0.001 |

FCR: Flexor carpi radialis; SD: Standard deviation

**Table 2.** Pearson correlation coefficients between different variables

| Variable | Upper limb length | Arm length | Age | FCR H-reflex latency |
|---|---|---|---|---|
| Upper limb length Pearson correlation | 1.000 | 0.913** | -0.248** | 0.647** |
| Arm length Pearson correlation | 0.913** | 1.000 | -0.213* | 0.574** |
| Age Pearson correlation | -0.248** | -0.213* | 1.000 | 0.103* |
| FCR H-reflex latency Pearson correlation | 0.647** | 0.574** | 0.103* | 1.000 |

* Correlation is significant at the 0.05 level; ** Correlation is significant at the 0.01 level; FCR: Flexor carpi radialis; That direct linear correlation between upper limb length and FCR H-reflex latency is stronger than correlation between arm length and FCR H-reflex latency; also it shows there is no significant correlation between age and FCR H-reflex latency

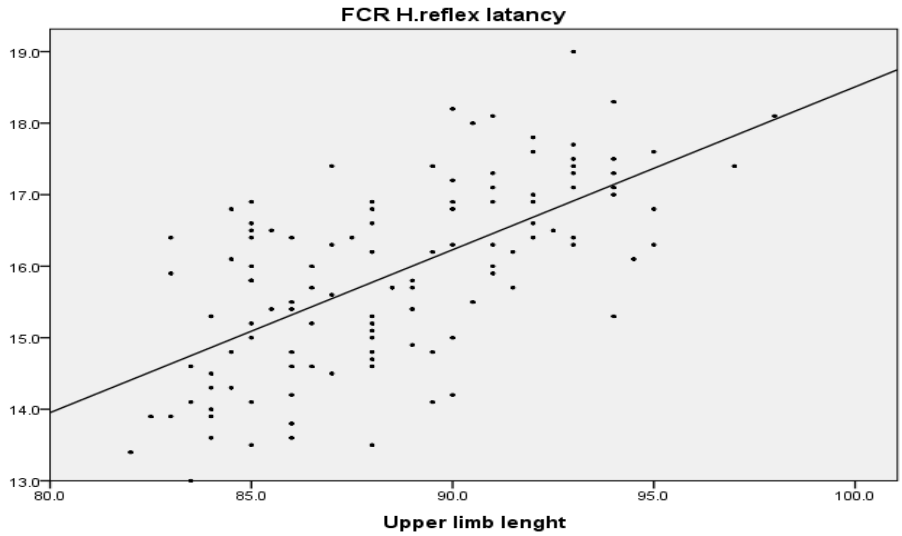


**Figure 2.** Regression line between flexor carpi radialis H-reflex and upper limb length
FCR: Flexor carpi radialis

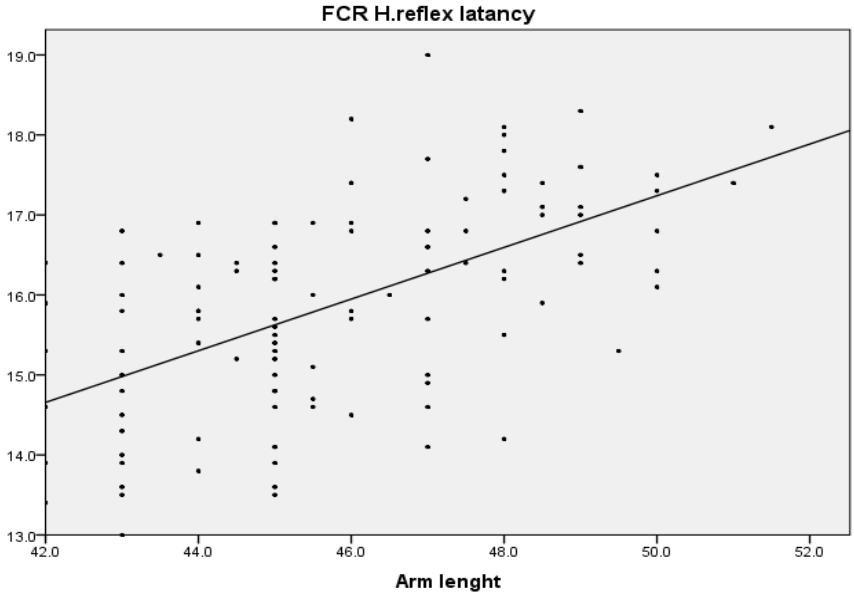


**Figure 3.** Regression line between flexor carpi radialis H-reflex and arm length
FCR: Flexor carpi radialis

## Discussion

Several studies have determined that FCR H-reflex is a valuable supplement to conventional conduction studies for diagnosis of upper limb pathologies.[12-15] In the present study, we investigated the correlation between different variables and FCR H-reflex latency and also defined two formulae to predict optimal FCR H-reflex latency based on upper limb length and arm length.

Consistent with the results of Ongerboer et al. we didn't find any significant relationship between FCR H-reflex latency and age.[21] However, Schimsheimer et al. found that it may be used to predict FCR H-reflex latency and inter-latencytime.[12] Based on pathophysiologic descriptions H-reflex latency would be expected to proportionally prolong in elderly because of its pathway seems to be affected by several age-related changes, involving both interneurons and the afferent and efferent tracks.[3,9,16,22] However maybe the effect of age is much less apparent on these parameters in subjects under 60 years-old as our subjects were in the range of 20-60 years old and the age-related changes are more important in older subjects.

H-reflexes have a long pathway that may be influenced by multiple factors and length of the limb may have a significant influence on its latency.[4] Based on anatomical pathway of H-reflex loop, this correlation between either thigh length and soleus H-reflex latency or upper limb length and FCR H-reflex latency are expectable. Several studies have investigated the relation between leg length, height and soleus H-reflex latency and found significant correlation.[17,18,23,24] Although a recent study did not find any relation between individual thigh length and soleus H-reflex latency.[25] Another found that in normal subjects regression equations demonstrate latencies of FCR and soleus H-reflexes can be predicted from limb length but equally accurately from body height.[14] Limited studies have shown the effect of upper limb length on FCR H-reflex latency,[12,13] but arm length has not been investigated before. In this study, we found a significant correlation between FCR H-reflex latency and both upper limb length and arm length; however this correlation was stronger between FCR H-reflex latency and upper limb length. This could be attributed to the fact that upper limb length include forearm region too, therefore FCR muscle inherent motor parameters can influence more apparently on H-reflex latency. However, more studies are needed to examine and compare the effects of these parameters on the FCR H-reflex latency.

As our results show, there are significant differences between FCR H-reflex latency as well as upper limb length and arm length among men and women. Thus besides intrinsic differences between characteristics of nerve fibers and muscles of males and females, it may conclude that upper limb and arm lengths have had significant effects on FCR H-reflex latency. Of course, other parameters such as arm/forearm diameter may have important influences that could be evaluated in future researches.

Two studies performed in 1985 and 1987 investigated clinical application of FCR H-reflex latency, and they found multiple formulae to estimate it based on different variables such as age, upper limb length and body height.[12,13] For instance one of these formulae is:

FCR H-reflex latency=1.29 + 0.01630 × limb length + 0.0270 × age ± 0.83

In comparison with our formula, it is obvious that for clinical application, they are not as much practical as ours. Additionally, they involved age and body height in their estimation but we did not. However the clinical usage and interpretation of the found formulae in this paper, should be explored by more researches.

While many segmental and supra-segmental parameters related to both physical and mental state of the individual can influence different parameters of H-Reflex and hence it seems that additional aspects can also be critical on prediction of FCR H-reflex latency.[8,26,27] These parameters should be considered and reviewed for better prediction which may include complete muscle relaxation and free of anxiety, effects of facilitatory maneuvers and antagonist muscle stimulation.

The findings of this study were interpreted in the light of previous studies, and one can say that this study will help to further determine various neurological diseases with different limb lengths. This research will also help in making a normative data for diagnosing various neurological diseases.

## Conclusion

The purpose of this study was to assess the relation between FCR H-reflex latency, upper limb length, arm length and age in healthy subjects. We found that although age has no correlation with FCR H-reflex latency but upper limb length and arm length are predictive values for estimating its latency.

## Conflict of Interests

The authors declare no conflict of interest in this study.

## Acknowledgments

This study was funded by Physical Medicine and Rehabilitation Department and financially supported by research chancellor of the Isfahan University of Medical Sciences as a research project numbered 393183. Our heartfelt thanks are extended to all the volunteers who so kindly agreed to participate in this study. The authors would like to thank Dr. Farnaz Dehghan (MD) and Mrs. Leila Izadi for their great help in editing and revision of the manuscript, and Mr. Akbar Hasanzade for his assistance, as statistical consultants (data analysis).

**How to cite this article:** Khosrawi S, Taheri P, Hashemi SH. Proposed equation between flexor carpi radialis H-reflex latency and upper limb length. Iran J Neurol 2015; 14(1): 41-6.

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Iranian Journal of Neurology

Clinical Note

Iran J Neurol 2015; 14(1): 47-49

# Mixed movement disorders revealing an atypical form of creatine deficiency syndrome

Received: 8 Sep 2014
Accepted: 13 Dec 2014

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**Keywords**
Movement Disorders, Creatine Deficiency Syndrome, Inborn Errors of Metabolism

## Introduction

Creatine deficiency syndromes (CDS) are inborn errors of creatine (Cr) biosynthesis characterized by mental retardation and severe language impairment.[1] Movement disorders, mainly dystonia have been described as additional features in CDS.[2] We report on an exceptional case of mixed movement disorders due to an atypical form of CDS. A.H. is a 26-year-old man, born to second-degree consanguineous parents with family history of mental retardation in maternal cousin. Pregnancy and delivery were normal. Psychomotor development was normal. At the age of 6 years, he presented with a progressive cervical and left-hand abnormal posture with myoclonic jerks. When first examined at the age of 20, he had myoclonic jerks in the left upper limb with cervical and left hand dystonia. The diagnosis of heredodegenerative disease (inborn errors of metabolism) was evoked because of the consanguinity, family history, age of onset and mixed movement disorders. Oriented biological and imaging investigations were performed. Brain magnetic resonance imaging was normal. Serum copper level was 90 (Normal range: 80-160); urine copper level was 14 (Normal range < 20 µg/24 h); ceruloplasmin level was 0.260 (normal level: 0.2-0.6 g/l). Genetic testing for DYT1 gene was negative. Peripheral blood smear was normal. Amino acids and organic acids abnormalities and remethylation disorders were excluded. Urinary Cr and guanidinoacetate (GAA) were analyzed by gas chromatography–mass spectrometry; they showed low level of Cr associated with a relatively high GAA concentration and low Cr/GAA ratio (0.45) whereas a normal value exceeds 1.[3] The diagnosis of mixed movement disorders due to an atypical form of CDS was made after the determination of intermediate GAA methyltransferase (GAMT) activity in lymphoblasts. Measurement of GAMT activity in lymphoblasts was performed according to Verhoeven et al.[4]

The clinical picture associated with the abnormal levels of Cr and GAA call the attention to CDS and particularly GAMT deficit for this patient. GAMT is the second enzyme in the process of Cr synthesis resulting from converting guanidinoacetate and S-adenosylmethionine into Cr and S-adenosylhomocysteine. Patients with GAMT deficiency exhibit complex clinical phenotypes with hyperkinetic movement disorders such as generalized dystonia and severe mental retardation with epilepsy.[1] Though reduced the GAMT activity in this patient, which was 0.107 nmol/h/mg protein (normal values: 0.29-0.31 nmol/h/mg protein), is equivalent to that reported for heterozygous parents.[5] As shown in



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figure 1, the GAMT activity of this patient was intermediate between that of the control subject and patients with a total GAMT deficiency, it was below the detection limit in GAMT deficiency patient (< 0.01 nmol/h/mg protein). Two hypotheses could be proposed to explain the association of a low Cr/GAA ratio with a partial deficit of GAMT activity and a clinical picture characterized by the presence of mixed movement disorders. The low Cr/GAA ratio could be attributed to a high endogenous consumption of Cr originating partly physiologically (50%) from high meat nutrition and partly (50%) from body synthesis. As for the partly deficient GAMT activity, it could be an atypical form of CDS with a non-ubiquitous GAMT deficiency. Additional explanations and hypothesis would be advanced once similar cases are studied.

## Conflict of Interests

The authors declare no conflict of interest in this study.


## Acknowledgments

None



**How to cite this article:** Nasrallah F, Benrhouma H, Kraoua I, Briand G, Omar S, Turki Ben Youssef I, et al. Mixed movement disorders revealing an atypical form of creatine deficiency syndrome. Iran J Neurol 2015; 14(1): 47-9.


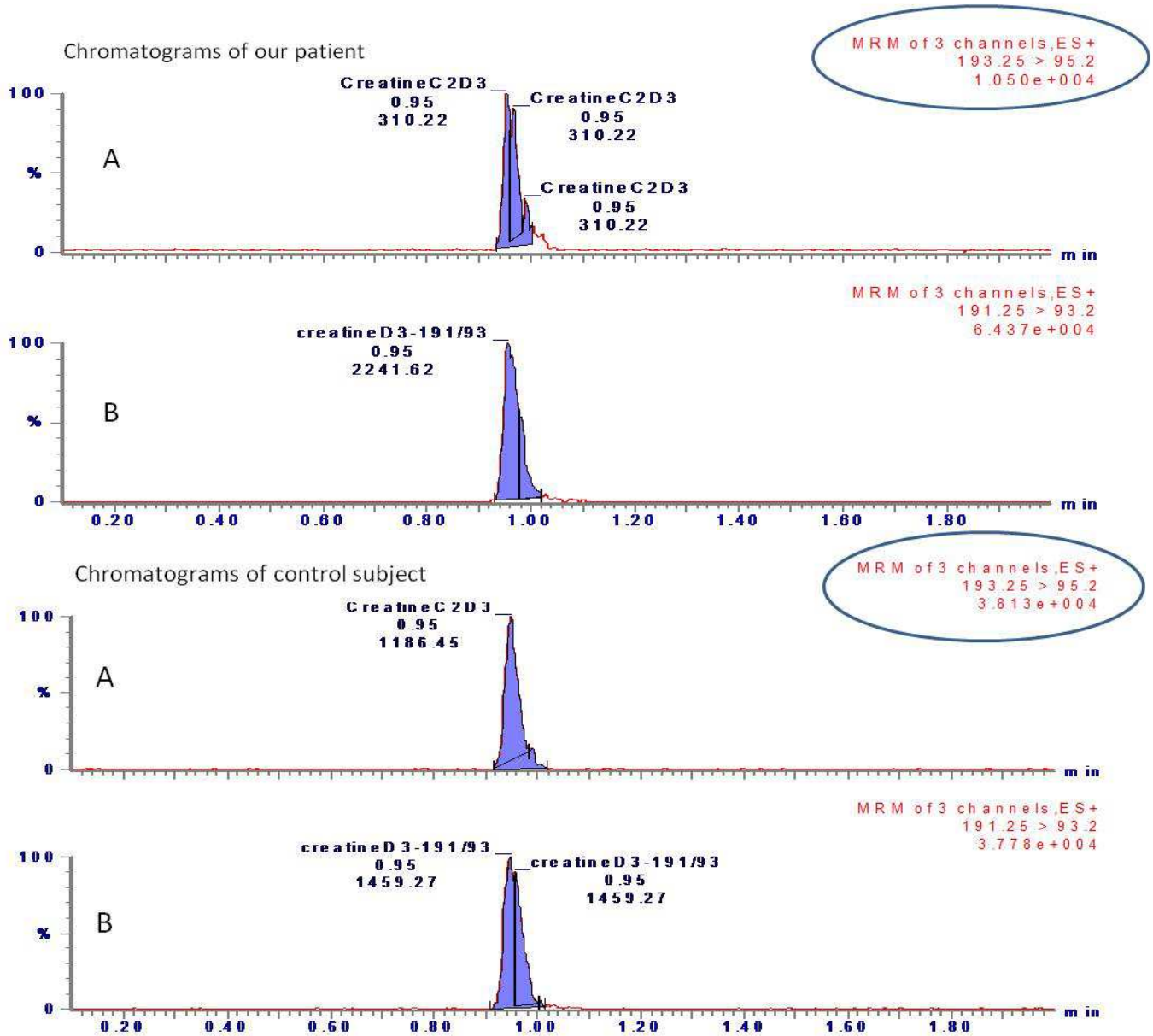


**Figure 1**. Chromatograms of patient (I), control subject (II) and guanidinoacetate methyltransferase patient deficiency (III) with an abundance = 1.05 $e^{+004}$, 3.813 $e^{+004}$, 7.294 $e^{+002}$ respectively. (A; chromatogram of [$^{13}C_2$-$^{2}H_3$]-creatine and B; chromatogram of internal standard D3-creatine)

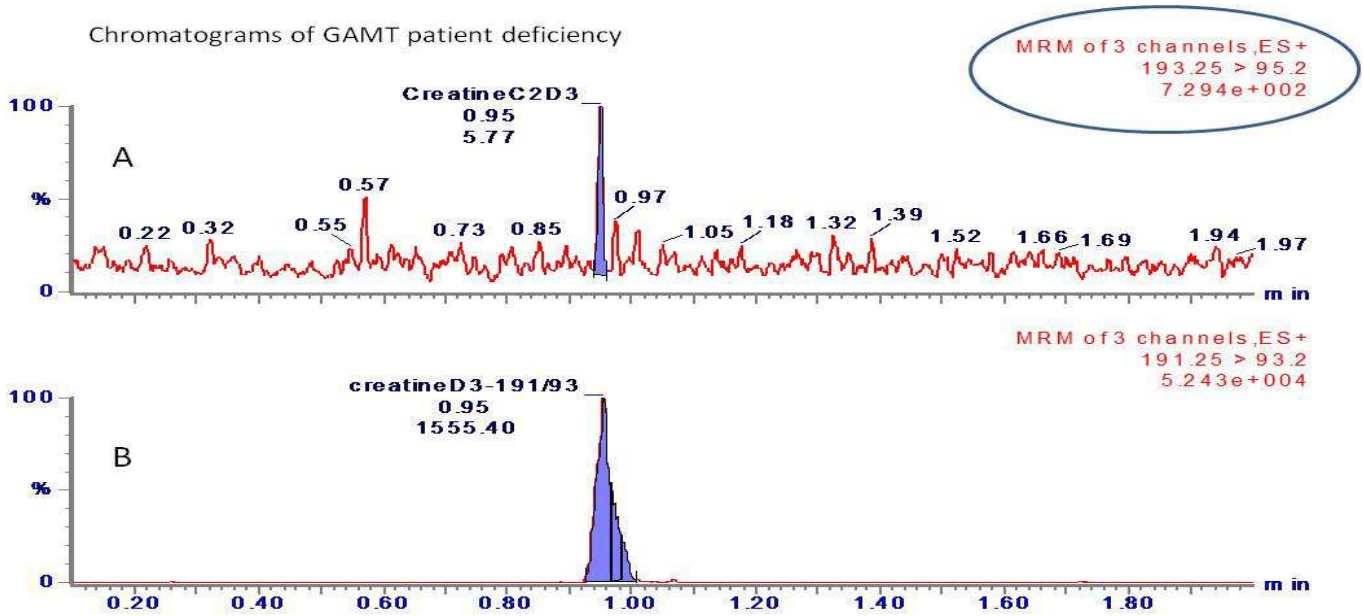


**Figure 1**. Chromatograms of patient (I), control subject (II) and guanidinoacetate methyltransferase patient deficiency (III) with an abundance = 1.05 $e^{+004}$, 3.813 $e^{+004}$, 7.294 $e^{+002}$ respectively. (A; chromatogram of [$^{13}C_2$-$^{2}H_3$]-creatine and B; chromatogram of internal standard D3-creatine) (Continue)

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Iranian Journal of Neurology

Letter to Editor

Iran J Neurol 2015; 14(1): 50-51

# Patent foramen ovale and stroke: Does presence of a migraine headache or any character of patent foramen ovale increase the risk of stroke?

Received: 27 Jul 2014
Accepted: 01 Sep 2014

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**Keywords**
Patent Foramen Ovale, Stroke, Migrain, Cerebrovascular

The etiology of ischemic stroke remains unidentified by routine diagnostic testing in about 40% of patients.[1] Patent foramen ovale (PFO) has been proposed as a possible cause of paradoxical cardioembolism and is found in 27% of unselected adults.[2] Nevertheless, the specific category of PFO bearers, who are prone to ischemic stroke, remains unidentified.[3] This study aims to determine the differences of some characters of PFO between patients with ischemic stroke in whom PFO was associated with another major source of stroke and those with PFOs as the primary cause of ischemic stroke. We compared and contrasted transesophageal echocardiography (TEE) and transcranial Doppler sonography findings between the patients with cryptogenic stroke and the patients with stroke of determined cause. A sunray transcranial Doppler ultrasound device version FD-T98II (Guangzhou Doppler Electronic Technologies, China) was used in all the patients. The device was set to a small sample volume of 10 mm in length and minimum possible gain to provide a setting optimal for micro-embolic signal (MES) discrimination from the background spectrum. The MES was defined as typical visible and audible (chirp, click), short duration (0.1 s) and high-intensity signals within the Doppler flow spectrum. The number of MES was counted using Valsalva maneuver (VM) and was graded as 0, I, II or III if 0, 1-9, 10-49 or ≥ 50 MES, respectively, were detected. TEE was performed to identify any potential cardiac source of embolism. Diagnosis of PFO was based on the presence of at least 3 bubbles in the left atrium after 4 cardiac cycles of the right atrium became opaque with contrast bubbles. The shunt was graded as I, II, or III if 3-9, 10-49, or ≥ 50 bubbles, respectively, were visualized in the left atrium. The maximal diameter of PFO was measured in the same view. Those PFOs with a diameter < 2 mm were considered as small, 2-4 mm as moderate, and ≥ 4 mm as large. In addition, we compared the conventional risk factors for ischemic



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stroke and the presence of migraine headache (MH) between these two groups.

Seventy-eight consecutive patients with PFO on TEE examination who had stroke for the first time, who presented with clinical signs of rapidly developing focal cerebral dysfunction and were admitted to a stroke center in Namazi Hospital, Shiraz, Iran, were recruited for this study. Infarct etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria.[4] Then, the patients with two or more causes of stroke other than PFO to the stroke of determined cause group and those who had PFO with or without atrial septal aneurysm (ASA) without any other causes for stroke to the cryptogenic stroke group were assigned.

Thirty-one patients (39.7%) had cryptogenic strokes and 47 (60.3%) had strokes of determined causes. There was no statistically significant difference between these groups with respect to sex, conventional risk factors for ischemic stroke, history of VM prior to stroke. In addition, there was no statistically significant difference in the presence of ASA, amount of cardiac shunt, PFO size and amount of MES between the groups. Patients with cryptogenic stroke were significantly younger (57.4 ± 13.9 vs. 65.1 ± 13.7, P = 0.018) and had less prior history of ischemic heart disease (6.5 vs. 27.7%, P = 0.020). Using the ROC curve, the cut-off point for the patients with cryptogenic stroke was less than 57 years of age.

MH was more prevalent in the patients with cryptogenic stroke, but the difference was not statistically significant (29% vs. 19.6%, P = 0.330). In the subgroup of patients with cryptogenic stroke, hypertension and ASA were significantly less frequent (P = 0.001 and P = 0.013, respectively) and MH was significantly more frequent (P = 0.028; odds ratio, 3.3; 95% confidence interval, 1.1-9.8). MH was significantly more prevalent among females in this age group (P = 0.004; odds ratio, 5.4; 95% confidence interval, 1.6-18.8). None of the patients with MH reported previous ischemic heart disease (P = 0.017), and none of them who were younger than 57 years of age were taking anti-platelet medications prior to stroke onset. Our findings suggest that PFO may play a more significant role in the pathogenesis of ischemic stroke in patients younger than 57 years of age. Patients with MH did not have bigger PFOs (P = 0.780), more cardiac shunting (P = 0.980) or more MES (P = 0.420), when compared to patients without past histories of MH.

We did not compare the characters of PFO in patients with or without MH and in patients younger than 57 years of age. Subjects with PFO who were suffering from MH and are younger than 57 years of age, especially in females may benefit from stroke-prevention measures. However, this hypothesis needs to be confirmed in future case-controlled clinical trials.


## Acknowledgments

The authors would like to thank the Center for Development of Clinical Research of Nemazee Hospital and Ms. Hosseini and Ms. Gholami of Shiraz Neuroscience Research Center for their kind assistance. This work was supported by a grant from Shiraz University of Medical Sciences (grant number: 88-4641).


## Conflict of Interests

The authors declare no conflict of interest in this study.


**How to cite this article:** Shariat A, Yaghoubi E, Aghasadeghi K, Rahimi A, Nemati R, Ashjazadeh N. Patent foramen ovale and stroke: Does presence of a migraine headache or any character of patent foramen ovale increase the risk of stroke? Iran J Neurol 2015; 14(1): 50-1.


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Iranian Journal of Neurology

Neurological Video

Iran J Neurol 2015; 14(1): 52

# Eating dystonia in a case of neuroacanthocytosis

Received: 28 Sep 2014
Accepted: 08 Oct 2014

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**Keywords**
Eating Dystonia, Neuroacanthocytosis, Video, Chorea, Movement Disorders

Neuroacanthocytosis is an autosomal recessive neurodegenerative disease, characterized by chorea, dementia, seizure, acanthocytes on peripheral blood smear and caudate atrophy on brain magnetic resonance imaging (MRI).[1,2]

These patients have severe orofacial dyskinesia and especially eating dystonia that causes severe eating problems and tongue and cheek biting. Eating or feeding dystonia, in combination with the above-mentioned signs and symptoms is characteristic of neuroacanthocytosis.[1-3]

Here, we present a video clip of a 40-year-old woman with typical eating dystonia .When she puts bolus in the mouth; dystonic movement of the tongue pushes it out (Video 1).

She had progressive choreiform movements especially orofacial dyskinesias since 10 years. Her brain MRI showed caudate atrophy and T2 and fluid-attenuated inversion recovery hyperintensity of caudate and putamens. On the peripheral blood smear, there were many acanthocytes.

Feeding dystonia is highly suggestive of neuroacanthocytosis and is a hallmark for this rare disease.[3]

## Conflict of Interests

The author declares no conflict of interest in this study.

## Acknowledgments

We would like to thank the patient for her cooperation.

**How to cite this article:** Rohani M, Shahidi Gh. Eating dystonia in a case of neuroacanthocytosis. Iran J Neurol 2015; 14(1): 52.

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Iranian Journal of Neurology

Special Article

Iran J Neurol 2015; 14(1): 53-58

# Neurolaw: A brief introduction

Received: 16 Jun 2014
Accepted: 27 Jul 2014

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**Keywords**
Brain, Human Behavior, Law, Legal Decisions, Legal Rules, Neurolaw, Neuroscience

**Abstract**
Neurolaw, as an interdisciplinary field which links the brain to law, facilitates the pathway to better understanding of human behavior in order to regulate it accurately through incorporating neuroscience achievements in legal studies. Since 1990's, this emerging field, by study on human nervous system as a new dimension of legal phenomena, leads to a more precise explanation for human behavior to revise legal rules and decision-makings. This paper strives to bring about significantly a brief introduction to neurolaw so as to take effective steps toward exploring and expanding the scope of law and more thorough understanding of legal issues in the field at hand.

## Introduction

The evolution of scientific theories is reliant on the integrity of their propositions through a comprehensive approach covering all aspects of subjects;[1] law is of no exception to this principle too. Unprecedentedly, legal effects and consequences are tied to neurological issues; hence an appeal to neuroscience would be inevitable for a better explanation for legal rules. Relationship between law and neuroscience; with brain lying in as their similar correlative factor, gives rise to neurolaw as an interdisciplinary field, offering more comprehensive, accurate approach to legal phenomena; that all put forward a more accurate evidence for legal process, and a fairer justice system; moreover, the expansion of both sciences is a matter of neurolaw.

There are plenty of cases in which neuroscientific data might be of significance to more accurately understand legal issues. This is why lots of neuroscientific evidences are increasingly reaching courts in a number of legal contexts in practice. Neurolaw would generate a better and wiser judicial, even legislative and executive system. Neuroscience achievements could change legal provisions, along with procedural law and customs, or even alter them radically to a new different one. Hence, this paper tries to give a brief introduction to neurolaw in order to take effective steps toward exploring and expanding the scope of the law and more thorough understanding of legal issues in the field at hand.

### *Neurolaw: the intersection of neuroscience and law*

Scientists with many investigations on the human brain have learned a tremendous amount about how it works, how it malfunctions, and how it can be repaired or altered. This emerging neuroscience, namely the scientific study of the nervous system, has already revolutionized medical practices. Neuroscience as a branch of biology is currently an interdisciplinary science that collaborates with other fields.[2] It also proved to be an immediate and powerful catalyst to understanding how the nervous system works and also exerts influence upon neurolaw.[3] Neurolaw is an attempt to know the relationship between law and brain by taking into account neuroscience findings.[4] In fact, neurolaw explores the effects of discoveries in neuroscience on legal rules.[5]

The most fundamental question among neuroscientists and lawyers is possibility of the relationship between law and neuroscience. Neuroscience is a natural science which based on experiment and indicative statements; while law is a humanities' science according to obligations, arising from the collective wisdom and abstract propositions. As more legal scientists believe, actually, law is a


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social phenomenon which has been formed by the social contract. Hence, law based on relative propositions, while neuroscience is on absolute ones. This leads our mind to real challenge that how it possible to propose and defend "neurolaw"? In fact, law is humans' creative[6] to regulate individuals' conducts insecure and excellence society, Instead of natural community in which there is no law, no state, people do whatever they want and security minimalized.[7] The ultimate goal of law is respecting to human dignity, in order to realization of humanity of a person and real justice; this purpose is achievable if we have better and more accurate rules in society, In other words, have a more fair legal system. Neuroscientific statements, with an open eye on neurological phenomenon, help law to have more accurate rules on this sense. More clearly, neurolaw shed light on justice way for law in its specific scientific area. For example, when legislators want to adopt a specific act, which related to punish offenders, or when judges want to decide about an accused, neuroscience achievements give precise glasses to lawyers, to have a more comprehensive view and consequently decide more equitable and fair legal decisions.

Drawing from neuroscience, neurolawyers try to understand human behavior, and will potentially shape future aspects of legal processes. Practically, they deliberate on human brain and nervous system image by medical technology scanning such as radiology, psychiatry, neurology, and clinical neuropsychology.[8] With these new imaging techniques, researchers interested in the function of the human brain were presented with an unprecedented opportunity to examine the neurobiological correlates of human behaviors. Essentially, neuroimaging methods create visual brain delineation and the imaging specialist interprets it.[9] Initially, neuroscience has been more exploited for Procedural law to stand criminal and civil liability complaint in court. Despite this pragmatic application of neuroscience, it has been applied to many legal subfields. Today, we are witnessing the development of neuroscientific considerations in various areas of law; such as Intellectual Property Law, Tort Law, Consumer Law, Health Law, Employment Law, Constitutional Law, and Criminal Law.[10] Even neurolaw perforate to scope of other related sciences; such as psychiatry, sociology, political science, behavioral ecology and economics that mainly emphasize on criminology.[11]

Neuroscience has shed light of enquiry on how the brain and certain mental processes can work, and it follows understanding structure and function of the brain. It gives us an insight into the mental processes that underpin human behavior as the law is primarily concerned with regulating people's behavior. It shapes an interdisciplinary science known as neurolaw. Because of huge differences among individuals' brains,[12] however, there is no direct mapping of mental function to specific areas of it.[13] This is a fundamental challenge in the neurolaw. Neurolaw scientists attempt to expose neuroscience results to legal rule and system; thereby, revise legal standards, norms, and conducts to a more accurate one. More precisely, the novel neuroscientific approach toward legal rules and consequences brings about a more perfect and better realization of legal effects; hereby, mutates the rules governing them so that a farrier legal system can be followed up.

## Neurocriminology

Neurocriminology is a sub-discipline of criminology that applies neuroscience techniques to probe the causes and cures of crime. Neurocriminology studies the makeup and composition of the brain and looks for correlations between characteristics of the brain and criminal behavior. The very rapid developments taking place in brain-imaging science are creating a new approach to our concepts of responsibility and retribution on the one hand, and understanding and mercy on the other.[14] Neurocriminology is documenting structural and functional brain impairments not just in antisocial, violent, and psychopathic individuals, but also in spouse abusers and white collar criminals. Neurocriminologists are proposing a neurodevelopmental contribution to crime causation. By neurocriminology researches, it is clarified that the brain circuits found to be impaired in offenders parallel the brain circuits found to underlie moral decision-making in controls. Recent researches in neurocriminology, are outlining implications not just for the field of criminology, but also for concepts of legal and moral responsibility, free will, and punishment. To this end, the legal implications of brain research, free will and the neural bases of antisocial or criminal behavior are of central importance. Understanding responsibility, free will, and punishment and their relationship profound debate brewed in neurocriminology; if the neural circuitry underling legality is compromised in offenders, is it morally and legally wrong of us to punish prisoners as much as we do? The relationship between belief in free will and third-party punishment of criminal norm violations have been the subject of great debates among philosophers, criminologists, and neuroscientists.

Free will is the often unspoken centerpiece of the criminal law, which presumes humans are responsible agents, who are free to choose to comply with social norms or violate them. While many texts discussing the forensic implications of neuroscience refer to cases where brain damage such as that caused by an accident, a tumor, or surgical resection is related to

alleged criminal behavior; this is the idea thoughts criminal, antisocial, sociopathic, or psychopathic behavior is linked to focal lesions of the brain.[15] Today, by neurocriminology studies, (Legal Responsibility) is far away from its classical sense. Neurocriminologists by considering, pondering and interpreting brain-imaging, endeavor to prove Relative offenders responsibility. There are multiple neuroscientific documents that imply the truth of their claims. To test their hypotheses, neurocriminologists combined functional magnetic resonance imaging (fMRI) with a third-party punishment task, asking healthy subjects to estimate how much punishment a hypothetical offender deserved for a set of prototypical offenses ranging across severity of crime from property destruction and theft to rape and murder.[16]

***A reflection on two main kinds of research in neurolaw***

Neurolaw is a relatively new and highly-interdisciplinary field while the Decade of the Brain[17] was first introduced to the health care and legal communities. The term neurolaw, among legal scholars, was first coined by Taylor et al.[18] More effectively, He raised the issue of it, with his prominent scientific paper entitled "Neuropsychologists and Neurolawyers."[18] Taylor's works during his career in academia[19] are of considerable significance in the research area of neurolaw, chiefly legal practice. Neuroscience and the law have interacted over a long history. Since 1990, however, neuroscientists and neurolawyers have often argued about eventuality of spreading neurolaw. Also, lecturers at several scientific conferences held in the United States, United Kingdom, France and Canada address this subject frequently.[20]

*Practical researches*

Neurolaw practical researchers are emphasizing on civil and criminal responsibility litigation and its practical challenges such as documenting neuroscientific data as evidence in the court room or neurolitigation problems. There exists much of legal process literature in the neurolaw. "Neuroscience and Legal Responsibility"[21] is one of the most leading recent works. It explores the field of legal responsibility by adopting a broadly compatibilist approach. The author argued that how neuroscience, psychology, and behavioral genetics should impact legal responsibility practices? This book mainly is challenging traditional conceptions of free will and legal liability. By a comparative analysis, among other works, "International Neurolaw: A Comparative Analysis"[22] compares the different legal systems and strategies that they offer for dealing with neurolaw implications; accordingly it is so important to understand different legal approaches to how revise legal system by new neuroscience results. Moreover, "Neurolaw for Trial Lawyers,"[23] "Law and Neuroscience: Current Legal Issues,"[24] "Neuroscience in the Courtroom,"[25] "A Primer on Criminal Law and Neuroscience,"[26] are another useful works offering aid in solving existing problems in legal practice. These works emphasize Procedural law and practical legal rule inspired by neurolaw. Practical neurolaw is most related to neurolitigation, applying these new criminal Procedural law standards in courtroom by judges and lawyers.

According to what was discussed, the main issues which have been proposed in neurolaw practical researches are as follows: neurolitigation challenges, neuroscientific Instruments for proving or compurgation legal responsibility, neurocriminology in Procedural law, standing neurolitigation, neuro advocacy and attorney, neuroscience and judgment, brain injury rights to appeal.

*Theoretical researches*

On the other hand, in the theoretical approach we understand the brain, its functions in the conceptual value. Such an approach is of particular importance in accentuating impact of brain on behavior. By this, we are recognizing new rules regulating these behaviors in the legal system. As neuroscientific technologies contribute to understanding of the mind, applying neuroscience discoveries in legal proceedings has also increased. Cognitive neuroscientists interrogate complex relationship between the mind and the brain. They do it rather by using new techniques such as fMRI and electroencephalography (EEG). And so, neuroscientific research and technology, by inference, drawn from these findings and increasingly sophisticated technologies, are being applied to legal system rules and processes in the legal field. In this regard, conceptual foundations of neurolaw are raised by the current extant philosophical questions. Theoretical researchers examine the arguments favoring the increased use of neuroscience in law. They ransack the means for assessing its reliability in legal proceedings. Also, theoreticians endeavor to integrate neuroscientific research into substantive legal doctrines. Thus, these effects are covering most aspects of theoretical issues to the practical ones. Maybe the most important books written on the basis of this research method, are as follows: "Minds, Brains, and Law: The Conceptual Foundations of Law and Neuroscience,"[4] "Neurolaw: Brain and Spinal Cord Injuries,"[27] "Law, Mind and Brain,"[28] "Materials on Neurolaw,"[29] "Law and the Brain"[30] and "The Neurobiology of Criminal Behavior."[31]

The major studies in neurolaw theoretical research field are as follows: feasibility of applying neuroscience results in legal system, concept of brain

and law, relationship between brain and law, development and technologies of neuroscience in legal system and future, brain disease and disordering legal orders, mental illness and brain injury affection on legal responsibility, right to privacy and brain-imaging, free will on third-party punishment, neuroscience and legal rights, neuroscience and legal freedoms, brain injury citizenship rights, individuals' right to security towards people with Neurological disease, revolution of legal rules by neurolaw theories.

***Some questions with which neurolawyers are encountering***

Neurolaw attempts to relate the brain to law as well as neuroethics to moral values; so the main question in this branch of neuroscience is how it is and will be used in the legal system? Scientists present a wide variety of possible neuroscience and law intersections.[32] As it appears, there are a number of distinct ways (including at a minimum in the contexts of Buttressing, Challenging, Detecting, Sorting, Intervening, Explaining, and Predicting) that neuroscience can offer value to law.[33] In practical sense, evidence suggests that the number of cases involving neuroscientific implications is rapidly increasing. Hereupon, this requires a spacious savvy in both spheres of law and neuroscience. Hence, many questions remain unanswered as to what extent can the brain affect human behavior that would bring about legal effect? and to have fairer and more equitable legal system, what legal rules and precedent should cover this aspect of conducts? How neuroscience should influence criminal and civil law?

Furthermore, Neurolaw encompasses ethical questions regarding nootropics, more commonly known as mind-enhancing drugs. Nootropics referred to as smart drugs which are memory, neuro, cognitive and intelligence enhancers (supplements, nutraceuticals, and functional foods that improve one or more aspects of mental function, such as working memory, motivation, and attention);[34] How will these enhancers affect individuals' legal rights in society? Will it become necessary to use an enhancing drug simply to remain competitive in society? Basically, do people have the right to experiment with substances to modify their own cognition?

With new technologies with which law has confronted, the rise of modern neuroscience expands deeply. It is necessary to be satisfied, on an acceptable level, whether we know enough to draw legally relevant conclusions. Does neuroscience tell us anything we don't already know from common sense or previous behavioral research? Essentially, are the scientific researchers and medical professionals capable of communicating their ideas in ways accessible for a legal audience? Are there some areas of law to which neuroscience may never be coherent? When we try to have access to the brain information via any Medical science technology, such as fMRI, are we in conflict with the right to privacy? What legal standards could be stated for these problems?

In conceptual sense, the issues are further complicated by the fact that legal doctrine and legal theory make use of our ordinary concepts of mind and mental life. Also, it is extremely difficult to address the relationship among Mind, Brain, and Law. Emphasizing this, neurolaw theorists by utilizing conceptual methodology and philosophical view, focus on the scope and contours being employed in claims involving neuroscience and law. Also, they are relying less on empirical, ethical and practical methods.[20] The what of the brain, mind, and law, is the main question arises in conceptual, methodological approach; understanding them in the true sense leads us to a mature abstract hindsight of behavior and conducts. Thereby, the path is paved to set of legal rules in order to regulate behaviors in society.

***Primary challenges ahead in Neurolaw***

Most neurolaw findings, besides philosophical, psychological and other related scientific approaches, are mainly based on neuro-medical technology experiments. Corollaries are achieved mostly according to the cognitive study of brain by brain-imaging. In this way, neuroscientists expound neuroscientific data that neurolawyers totally link them to legal effects. An instance is compliant brain-scanning to proving his /her civil or criminal responsibility against the plaintiff who claims it in the tribunal. Based on hermeneutic Interpretation and different perceptions of behavior, the most dreadful problem here is a possible and limited commentary on neuroscientific data and neuro-images.

Neuroscience and law are very different disciplines in nature from laboratory to the courtroom. Discrepancy of language is a critical issue facing neurolaw scientists. It is pretty obvious, neurolawyers are being accosted with many words have slightly varying meanings, or they can be used as a different sense in both sciences. Proof of claim in law must be accurate, reasonable and well-documented. So real problem which arises is probable or almost certain neurological inferences which neurolawyers try to close them to evidence recognized by law;[35] that is main courtroom problem; this ambiguity of thought extended to state rules or legal processes. All causes a situation in which the cognitive neuroscience influence on the legal field will be so complicated and difficult.

Furthermore, there is an overriding challenge between neuroscience and Human Rights as a branch of Public Law. Neuroscientists strive to get access to neuroscientific data by brain-scanning (such as MRI,

FMRI, and EEG), while human rights defenders prevent them. Typically such a quarrel is occurring by assertion of the right to privacy or maybe the right to health; just as conflicting norms between medical law and medical test requirements are originated.

These all lead us to having more concentration on both neuroscience and law to find an appropriate solution and direction between their propositions; this will give origination to neurolaw rules and principles which help both legal and neuroscientific understanding of human behavior. We primarily know: "1- better legal outcomes promote better clinical outcomes for patients with neurological injury; 2- successes in neurolitigation is dependent largely upon the quality and quantity of expert evidence; 3- mutual cooperation among concerned professional enhances the probability of successful neurolitigation; 4- to be successful, clinical and legal professionals require litigation literacy."[36].

## Conclusion

The law is not valuable per se. Instead, it is instrumentally used to regulate human behavior due to getting hold of justice; for this purpose we need a comprehensive understanding of legal rules from different scientific standpoints, to be recognized by legal system; one of these most effective sciences which gives hand to law mainly in practical sense, is neuroscience. Neuroscience, exploring brain functions and structures, throws light on the way to better understanding of human behavior. The blend of these two subject-matters (neuroscience and law) has paved the way for neurolaw, in 1990's. There are two main methods in the neurolaw: theoretical and practical. Until now, most of the neurolawyers have been working on brain functions and neuroscientific data to have a more accurate and fairer justice system, keeping an open staring eye upon successful neurolitigation over several cases in courtrooms. These all highlighted the practical aspect of the subject-matter. However, there were uncertainties about neurolaw but now neurolaw scientists have properly found out that neuroscientific achievements can assist law to have a more reliable decision and rules, and it has shown itself in the field of Procedural law specially civil and criminal responsibility. Of course, neurolaw, while crucial in our legal studies, would help us to apply medical knowledge and technology in the legal area to achieve a more equitable legal system. So to prove liability, to improve the knowledge of the judge with respect to claims, to expand the scope of law, to have a better perception of legal phenomena, even to comprehend the brain and mind to revise the concept of right and many more are windows opened toward our scholarship through neurolaw. It will even associate with Islamic jurisprudence propositions such as those which are discussed in criminal punishments, responsibilities, judicial issues, etc.

## Conflict of Interests

The authors declare no conflict of interest in this study.


## Acknowledgments

None



**How to cite this article:** Petoft A. Neurolaw: A brief introduction. Iran J Neurol 2015; 14(1): 53-8.


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