# Young Stroke due to Multiple Risk Factors in a Patient with Rheumotoid Arthritis: A Case Report

# Romatoid Artritli Bir Hastada Multipl Risk Faktörleri Sebebiyle Oluşan Genç İnme: Olgu Sunumu

**Berke ARAS[1], Volkan YILMAZ[2], Fatma AVŞAR ERTÜRK[3]**

[1]Kastamonu Rehabilitation Centre, Physical Rehabilitation Medicine Clinic, Kastamonu
[2]Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Physical Rehabilitation Medicine Clinic, Ankara
[3]Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Neurology Clinic, Ankara

**Abstract**
The risk factors of stroke in young population are associated with large or small vessel diseases, cardiac diseases, hematologic disorders and genetic disorders. Rheumatologic disorders such as rheumatoid arthritis may also be associated with increased stroke risk. Furthermore, non steroid anti-inflammatory drugs and steroids which are widely used for the medication of these disorders may contribute to risk of stroke. In this paper, a 44 years old female patient with stroke and comorbid rheumatoid arthritis who has additional stroke risk factors including methyl tetrahydrofolate reductase gene mutation, low vitamin B12 level, tromobocytosis and methotrexate therapy was investigated.
**Keywords:** Methotrexate, Methyl Tetrahydrofolate Reductase, Rheumatoid Arthritis, Stroke

**Öz**
Genç hastalarda inme ile ilgili risk faktörleri küçük ya da büyük damar hastalıkları, kalp hastalıkları, hematolojik ve genetik bozukluklardır. Romatoid artrit gibi romatolojik hastalıklar da ayrıca artmış inme riski ile ilişkili olabilir. Buna ek olarak, bu hastalıklarda sıklıkla kullanılan non-steroid antiinflamatuar ilaçlar ve steroidler de inme risk faktörleri arasında sayılabilir. Bu vakada, komorbid romatoid artrite ek olarak metil tetrahidrofolat reduktaz gen mutasyonu, düşük B12 vitamin seviyesi, trombositoz ve metotreksat tedavisi gibi ek inme risk faktörleri olan 44 yaşında inmeli kadın hasta sunulmuştur.

**Anahtar Kelimeler:** Metotreksat, Metiltetrahidrofolat Reduktaz, Romatoid Artrit, İnme

## Introduction

Although stroke is known to be a disease for elderly, cases under age of 45 years are accepted young stroke patients. The causes of stroke in young population are more diverse than elderly and can be associated with several risk factors including large or small vessel diseases (dissection, toxic and infectious vasculopathy, premature atherosclerosis, vasculitis associated disorders like rheumatoid arthritis, systemic lupus erythematosus, central nervous system arteritis and Takayasu arteritis), cardiac diseases (congenital heart disease, rheumatoid valve disease, mitral valve prolapsus, endocarditis and arrhythmias), hematologic disorders (sickle cell disease, leukemia, thrombocytosis, polystemia vera, thrombotic thrombocytopenic purpura, hypercoagulation states like antiphospholipid antibody syndrome, deficiency or resistance to antithrombin III or protein C or protein S) and genetic disorders (homocystinuria, Fabry's disease, pseudoxhantoma elacticum and MELAS syndrome) (1).

| | ORCID No |
|---|---|
| Berke ARAS | 0000-0003-1944-2477 |
| Volkan YILMAZ | 0000-0002-7744-4123 |
| Fatma AVŞAR ERTÜRK | 0000-0002-0238-8008 |

Başvuru Tarihi / Received: 21.03.2019
Kabul Tarihi / Accepted : 08.07.2019

Adres / Correspondence : Berke ARAS
Kastamonu Rehabilitation Centre, Kastamonu

e-posta / e-mail : drberkearas@gmail.com

Rheumatoid arthritis (RA) is known to be associated with several complications including cardiovascular and cardiovascular related disease (2).

In the present paper, we reported a young stroke patient with multiple risk factors: RA, methyl tetrahydrofolate reductase (MTHFR) gene mutation, low vitamin B12 level, tromobocytosis and methotrexate therapy.

## Case

The patient was 44 years old female and consulted to our inpatient clinic suffering from being unable to use her left leg and arm. The history of the patient goes back three months ago when she had suffered from sudden unconsciousness and weakness at left half of the body. Brain magnetic resonance imaging (MRI) of the patient revealed acute perfusion loss in right middle cerebral artery (MCA) watershed area, eudema next to temporoparietofrontal lobe and diagnosed as ischemic cerebrovascular infarct therefore the patient received thrombolytic treatment. The platelet level of the patient was 636x103/μL when she was diagnosed as cerebral infarction. Diagnostic hematological tests of the patient exhibited homozygous methyl tetra hydro folate reductase (MTHFR) 1298 gene mutation but MTHFR 677, prothrombin and factor V leiden mutation tests were normal. Anticardiolipin and antiphospholipid Ig G and M levels were negative. Echocardiography and doppler ultrasound imaging of vertebral arteries were also normal. The medical

history of the patient include chronic hepatitis B, iron deficiency anemia and RA. The patient was using rituximab, methothoraxate (MTX), folic acid, acetyl salisilic acid and tenofovir treatment. The upper extremity was compatible with brunnstrom stage 2, hand with brunnstrom stage 1 and lower extremity with stage 5 in her neurological examination, she had no swollen or tender joint and the other systematic examinations were normal at initial visit. Patient was hospitalised for rehabilitation programme. Laboratory results after her hospitalisation were as follows:

Haemoglobin: 10.3 g/dl (13.2-17.3), platelet: $484x10^3$, alanine aminotransferase (ALT): 69 IU/L (3-50), vitamin B12: 183 pg/mL (126.5-505), folic acid: 11 ng/mL (2.5-24.8), homocysteine: 26.7 µmol/L (0-13), factor 8: 119.7% (0-150), protein S: 49.5% (60-130), protein C: 108% (70-143), activated protein C resistance ratio: 0.9 (0.65-1.54), antithrombin III activity: 93.9% (75-125), factor 5: 148% (70-120), cyclic cytrulinated protein (CCP): 9.5 IU/mL anti HBc Ig G was positive. A rehabilitation procedure including range of motion and stretching exercises, quadriceps and hamstring strengthening exercise with isokinetic exercise device, occupational therapy, walking exercises in parallel rod, and electrical stimulation for upper and lower extremities was provided for the patient. The upper extremity was compatible with brunnstrom stage 3, hand was compatible with stage 2 and lower extremity was compatible with stage 5 and she was walking with a canadian support when she was discharged from our rehabilitation unit.

## Discussion

Young stroke is associated with well defined risk factors. In our case, the cause of stroke may be attributed to cumulative effect of several risk factors.

Firstly a methyl tetrahydrofolate reductase (MTHFR) gene mutation was demonstrated in our case. Reduction of MTHFR enzyme activity increases the pool of 5,10 methylenetetrahydrofolate (5,10-methylene THF) at the expense of the pool of 5-methyltetrahydrofolate (5-methyl THF), which is used as a methyl group donor in the synthesis of methionine from homocysteine (3). MTHFR gene locus is located in chromosome 1p36.3 in humans (4) and ischemic stroke is shown to be associated with C to T transition at nucleotide 677 (C677T) in exon 4, which results in an alanine (Ala) to valine (Val) substitution on MTHFR enzyme (5). Presence of this substitution results in decreased enzyme activity and increased homocysteine level which is an independent risk factor for stroke (6). Furthermore, we found a low vitamin B12 level in the patient which is a co-factor for MTHFR, suggesting high homocysteine levels (7). MTX usage may be addressed for hyperhomocysteinemia (8). Folic acid supplementation has been shown to alleviate hyperhomocysteinemia for this instance and our patient was using folic acid treatment (9).

Secondly, our patient had a trombosytosis. Hematologic disorders are one of the unusual causes of stroke (6). In young adults, the prevalence of acute stroke in association with hematologic disorders varies up to 7% (10). Acute stroke due to tromobocytosis is unexpected under platelet counts lower than 1000x109/L (11) but our patient had a platelet count of 800x103/L suggesting a reactive trombocytosis to RA.

At least RA is another risk factor for stroke in our patient. The link between RA and stroke has been previously discussed from the aspect of different diverse causes such as aterotrombosis, thromboembolism, hemorrage and atrial fibrillation in the literature (12). However, data about the direct relationship between RA and stroke is still controversial. Nadreishvili et al (13) have reported three fold increased risk of stroke in patients with RA while Holmqvist et al (12) reported lower risk (1.2 fold). Inflammation has been proposed to be the the potential factor for atherosclerosis process leading to stroke and TNF is the key driver of this process (14). The patient we have presented in this paper was taking rituximab and MTX combination therapy. Data about the effect of biological DMARDs including TNF inhibitors on stroke is poor and controversial. No significant association between stroke and TNF inhibitor treatment was found in a large cohort (15). Similarly, Lindhardesen et al (16) have found no difference at stroke risk in rituximab+MTX treatment versus placebo+MTX. Non steroidal anti-inflammatory drugs (NSAID) and steroids have been shown to be associated with increased stroke risk (17,18). From medical history of our patient we assigned that she had previously used several NSAID and steroid drugs.

In conclusion, young stroke is associated with several risk factors including hematologic abnormalities, inflamatuar diseases, vitamin B12 deficiensies, use of DMARDs. RA may contribute to risk of stroke with several aspects such as vascular injury regarding to inflammation, reactive thrombocytosis, NSAID and steroid usage. We recommend to focus on potential risk factors of stroke in patients with RA. Especially in young patients with potential risk factors, patients should be evaluated carefully and treatment options should be considered for contribution with stroke risk factors.

**Written Consent:** Written consent was taken from patient on 12.12.2018.

## References

1. Kes VB, Zavoreo I, Demarin V. Etiology and diagnostic work-up in in young stroke patients. Periodicum Biologorum. 2012;114(3):355-9.
2. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med. 2004;116(5):305–11.
3. Toyoda K, Uwatoko T, Shimada T, et al. Recurrent small-artery disease in hyperhomocysteinemia: widowers' stroke syndrome? Intern Med. 2004;43(9):869-72.
4. Goyette P, Sumner JS, Milos R, et al. Human methylenetetrahydrofolate reductase: isolation of cDNA, mapping and mutation identification. Nat Genet. 1994;7(2): 195-200.
5. Frosst P, Blom HJ, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet. 1995;10(1):111-3.
6. Somarajan BI, Kalita J, Mittal B, Misra UK. Evaluation of MTHFR C677T polymorphism in ischemic and hemorrhagic stroke patients. A case-control study in a Northern Indian population. J Neurol Sci. 2011;304(1-2): 67-70.
7. Huang YC, Chang SJ, Chiu YT, Chang HH, Cheng CH. The status of plasma homocysteine and related B-vitamins in healthy young vegetarians and nonvegetarians. Eur J Nutr. 2003;42(2):84–90.
8. Refsum H, Helland S, Ueland PM. Fasting plasma homocysteine as a sensitive parameter of antifolate effect:A study of psoriasis patients receiving low dose methotrexate treatment. Clin Pharmacol Ther. 1989;46(5):510-20.
9. Morgan SL, Baggot JE, Vaughn WH, et al. The effect of folic acid supplementation on the toxicity of low-dose methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 1990;33(1):9-18.
10. Sandercock PAG, Warlow CP, Jones LN, Starkey IR. Predisposing factors for cerebral infarction: the Oxfordshire Community Stroke Project. Br Med J. 1989;298(6666):75-80.
11. Ross Russell RW, Wade JPH. Haematological causes of cerebrovascular disease. In: Toole JF, ed. Handbook of Clinical Neurology: Vascular Diseases. Amsterdam, Netherlands: Elsevier Science Publishers BV; 1989:463-81.
12. Holmqvist ME, Klareskog L, Alfredsson L, Askling J. Stroke in rheumatoid arthritis: (when) is there an increased risk? Ann Rheum Dis. 2010;69(3):109.
13. Nadareishvili Z, Michaud K, Hallenbeck JM, Wolfe F. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. Arthritis Rheum. 2008;59(8):1090–6.
14. Hallenbeck JM. The many faces of tumor necrosis factor in stroke. Nat Med. 2002;8(12):1363–8.
15. Low ASL, Lunt M, Mercer LK, et al. Association between ıschemic stroke and tumor necrosis factor ınhibitor therapy in patients with rheumatoid arthritis. Arthritis & Rheumatol. 2016:68(6);1337–45.
16. Lindhardesen J, Ahlehoff O, Gislason GH, et al. Risk of atrial fibrillation and stroke in patients with rheumatoid arthritis: Danish nationwide cohort study. BMJ. 2012;8;344:e1257
17. Bowman TS, Gaziano JM, Kase CS, Sesso HD, Kurth T. Blood pressure measures and risk of total, ischemic, and hemorrhagic stroke in men. Neurology. 2006;67(5):820–3.
18. Solomon DH, Avorn J, Katz JN, et al. Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. Arthritis Rheum. 2006;54(12):3790–8.