CRYPTOGENIC ISCHEMIC STROKE IN A YOUNG ADULT ASSOCIATED WITH *MTHFR* GENE POLYMORPHISMS: A CASE REPORT.

Abstract:

Background: Ischemic stroke in young adults requires comprehensive etiological investigation because of the wide range of potential underlying mechanisms. Hyperhomocysteinemia has been associated with cerebrovascular risk, while the clinical significance of common methylenetetrahydrofolate reductase (MTHFR) variants remains debated.

Case Presentation: A 23-year-old man with no significant medical history was admitted for sudden-onset headache, vertigo, balance disturbances, and left-sided hemiplegia. Brain computed tomography and magnetic resonance imaging revealed an acute left cerebellar infarction in the territory of the posterior inferior cerebellar artery (PICA), with collateral vascular circulation and a small petechial hemorrhagic transformation. Cardiac investigations, vascular imaging, and testing for selected thrombophilic and autoimmune conditions did not identify a definitive conventional cause. Genetic testing was negative for the factor V Leiden (F5) and prothrombin (F2) G20210A variants. Analysis of MTHFR identified homozygosity for the A1298C variant and no detectable C677T variant. Plasma homocysteine was elevated.

Discussion: The coexistence of hyperhomocysteinemia and homozygous MTHFR A1298C raises questions about the contribution of homocysteine metabolism to the cerebrovascular event. However, the A1298C variant does not generally cause substantial hyperhomocysteinemia by itself, and the observed association cannot establish causality. Other determinants of homocysteine concentrations, including folate and vitamin B12 status and renal function, should be considered.

Conclusion: This case highlights the importance of comprehensive etiological assessment in young adults with ischemic stroke. The clinical significance of the homozygous MTHFR A1298C variant should be interpreted cautiously, and the management of hyperhomocysteinemia should be guided by its underlying causes and established principles of secondary stroke prevention

Key words:-
Ischemic stroke; Young adult; MTHFR; A1298C; Hyperhomocysteinemia; Cryptogenic stroke; Case report.

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1. INTRODUCTION:

Ischemic stroke is a major cause of mortality and long-term disability worldwide. Although its incidence increases with age, it also occurs in young adults, in whom identifying the underlying mechanism is particularly important for treatment and secondary prevention. Etiologies in this population are heterogeneous and include cervical artery dissection, cardioembolism, selected hematological disorders, inflammatory diseases, and conventional cardiovascular risk factors [1,2].

The etiological investigation of ischemic stroke in young adults requires an individualized approach integrating clinical assessment, brain and vascular imaging, cardiac investigations, and appropriate laboratory testing. When initial investigations fail to identify a definite cause, further assessment may be necessary to detect potentially treatable conditions [1,2].

Hyperhomocysteinemia, defined as an elevated plasma concentration of homocysteine, has been investigated as a potential contributor to vascular disease. Homocysteine is a sulfur-containing amino acid involved in methionine metabolism. Its plasma concentration may be influenced by folate and vitamin B12 status, renal function, nutritional factors, and genetic variation affecting one-carbon metabolism. Observational studies and meta-analyses have reported associations between elevated homocysteine and ischemic stroke, although the magnitude and clinical implications of this association remain subjects of investigation [3,4].

The MTHFR gene encodes methylenetetrahydrofolate reductase, an enzyme involved in folate metabolism and the remethylation pathway that converts homocysteine to methionine. Two commonly studied variants are C677T, designated c.665C>T in current coding-DNA nomenclature, and A1298C, commonly designated c.1298A>C in older nomenclature and c.1286A>C on transcript NM_005957.4. These variants have different biochemical effects and should not be considered interchangeable.

Although the C677T variant has been extensively investigated in relation to homocysteine concentrations and vascular risk, the clinical significance of A1298C remains less straightforward. Meta-analyses have reported associations between A1298C and stroke susceptibility in some populations, but findings are heterogeneous and do not establish that this variant causes stroke in an individual patient [5,6]. Furthermore, the American College of Medical Genetics and Genomics has emphasized the limited clinical utility of routine MTHFR polymorphism testing in the evaluation of thrombophilia [7].

Management of hyperhomocysteinemia requires consideration of potentially reversible causes, including documented vitamin deficiencies and renal impairment. However, lowering homocysteine concentrations does not necessarily translate into a demonstrated reduction in recurrent stroke. Randomized trials and current secondary prevention guidance do not support routine B-vitamin supplementation solely to prevent recurrent stroke in all patients with hyperhomocysteinemia [1,8,9].

We report a case of acute cerebellar ischemic stroke in a young adult with elevated plasma homocysteine, homozygosity for the MTHFR A1298C variant, and no detectable MTHFR C677T variant. Testing for the factor V Leiden and prothrombin G20210A variants was negative. This report describes the clinical, radiological, laboratory, and genetic findings and discusses their possible significance without assuming a causal relationship.

2.CASE PRESENTATION AND INVESTIGATIONS:

2.1. Clinical Presentation

A 23-year-old man with no significant medical history and no known history of substance use presented to the emergency department with sudden-onset neurological symptoms, including an unusual headache, rotational vertigo, balance disturbances, and left-sided hemiplegia. Neurological examination confirmed left-sided motor impairment, described in the clinical record as predominantly spastic, together with cerebellar signs.

2.2. Brain and Vascular Imaging

Initial brain computed tomography (CT), followed by magnetic resonance imaging (MRI), revealed an acute left cerebellar ischemic lesion in the territory of the posterior inferior cerebellar artery (PICA). Diffusion-weighted imaging and T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences confirmed the infarction.

Vascular imaging, including magnetic resonance angiography and CT angiographic imaging was performed to investigate a possible arterial cause. No vertebral or carotid artery dissection was identified. Collateral vascular

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circulation was also reported in the affected territory. A small focal petechial hemorrhagic transformation was observed within the infarct (Figures 1–3).

These imaging findings characterized the cerebral lesion but did not, by themselves, establish the underlying mechanism of the stroke.

Figure 1. Brain CT scan

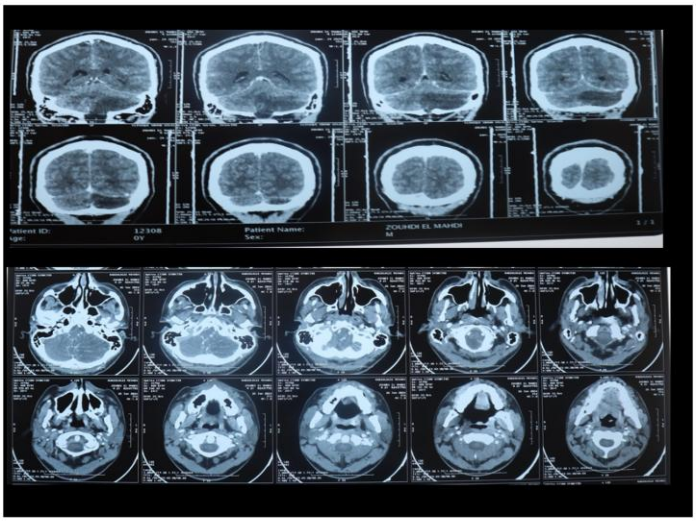
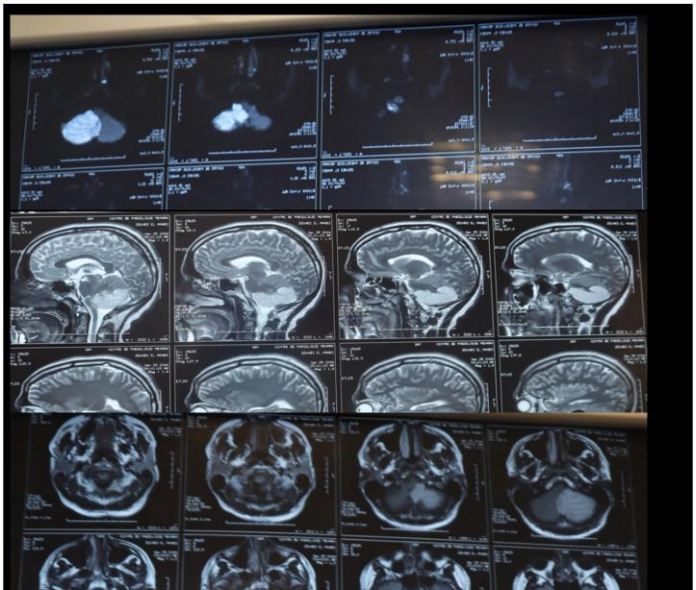


Figure 2. Brain MRI



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Hematological and autoimmune investigations. Testing for selected thrombophilic conditions did not reveal deficiencies in protein C, protein S, or antithrombin III. Genetic testing was negative for the factor V Leiden variant in F5 and the prothrombin G20210A variant in F2. Testing for antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein I antibodies, was negative.

Metabolic investigations. Fasting plasma homocysteine measurement revealed an elevated concentration, consistent with hyperhomocysteinemia. The exact concentration and laboratory reference interval should be reported if available. The assessment of potential contributing factors should include folate and vitamin B12 concentrations and renal function, where these data have been obtained.

Genetic investigations. Genetic analysis of MTHFR identified homozygosity for the A1298C variant, with no detectable C677T variant. The result was reported as MTHFR c.1298A>C homozygous in the original laboratory nomenclature. Because transcript-specific nomenclature may designate this variant c.1286A>C, the reference transcript and HGVS description should be verified against the original genetic laboratory report before publication.

The genetic investigation therefore identified a homozygous MTHFR A1298C variant in the absence of the C677T variant. Testing for F5 Leiden and F2 G20210A was negative.

2.4. Summary of the Principal Findings

The etiological investigation did not identify a definitive conventional cardiac or arterial cause of the ischemic event. The principal findings were an acute left cerebellar infarction in the PICA territory, elevated plasma homocysteine, homozygosity for the MTHFR A1298C variant, and absence of the MTHFR C677T, F5 Leiden, and F2 G20210A variants.These findings raise the possibility of a contribution from homocysteine metabolism but do not establish that the MTHFR variant caused the hyperhomocysteinemia or the stroke. The case is therefore best interpreted as an ischemic stroke of undetermined etiology following the investigations described, with associated metabolic and genetic findings.

2.5. Ethical Considerations

Written informed consent was obtained from the patient for genetic testing and for the use and publication of relevant clinical, laboratory, and imaging data. The case was prepared in accordance with the principles of the Declaration of Helsinki and applicable ethical requirements.

3. DISCUSSION:

3.1. Ischemic Stroke in Young Adults and the Etiological Challenge

Ischemic stroke in young adults requires a broad diagnostic approach because the underlying mechanisms differ from those commonly encountered in older populations. Potential causes include arterial dissection, cardioembolism, selected hematological disorders, inflammatory conditions, and conventional vascular risk factors [2,10].

In the present case, cardiac assessment, vascular imaging, and the reported hematological and autoimmune investigations did not identify a definitive conventional cause. Nevertheless, a negative initial workup does not exclude every possible etiology. The classification of a stroke as cryptogenic or of undetermined etiology should reflect the investigations actually completed and the criteria used to classify the event.

The clinical and radiological findings confirmed an acute cerebellar infarction in the PICA territory. The associated collateral circulation and petechial hemorrhagic transformation are relevant imaging observations, but neither finding independently identifies the mechanism of the stroke or demonstrates a relationship with the MTHFR variant.

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3.2. Hyperhomocysteinemia and Cerebrovascular Risk

Hyperhomocysteinemia has been associated with vascular disease in observational studies. A meta-analysis by Kelly et al. reported an association between elevated homocysteine and ischemic stroke, although the results for the MTHFR C677T genotype did not establish a statistically significant association in that analysis [3]. Hankey and Eikelboom also reviewed epidemiological and experimental evidence concerning homocysteine and stroke, highlighting the complexity of interpreting this relationship [4].

In the present case, the elevated plasma homocysteine concentration is an important biochemical finding. However, its interpretation requires the exact concentration, the laboratory reference interval, and an assessment of potential contributing factors. Folate or vitamin B12 deficiency, impaired renal function, nutritional factors, and other metabolic conditions may influence homocysteine concentrations.

The available information does not establish whether the hyperhomocysteinemia preceded the stroke, resulted from a persistent metabolic abnormality, or was related to a reversible contributing factor. Therefore, its contribution to the cerebrovascular event remains plausible but unproven.

3.3. Homozygous MTHFR A1298C and Absence of C677T

The principal genetic finding in this case is homozygosity for the MTHFR A1298C variant, with no detectable C677T variant. This distinction is important because much of the historical literature on MTHFR and stroke has focused on C677T rather than A1298C.

The A1298C variant affects the MTHFR enzyme, but its biochemical consequences differ from those of C677T. In particular, A1298C alone does not generally produce substantial hyperhomocysteinemia, even in homozygous individuals [7,11]. Accordingly, the elevated homocysteine concentration observed in this patient should not automatically be attributed to the A1298C genotype. Other metabolic and environmental factors should be investigated where possible.

The association between A1298C and stroke susceptibility has been examined in systematic reviews and meta-analyses. Kumar et al. reported an association between A1298C and stroke in certain populations, with differences according to ethnicity and genetic model [5]. Dong et al. subsequently reported statistically significant pooled associations between A1298C and stroke susceptibility, while also identifying heterogeneity across the included studies [6].

These population-level findings do not demonstrate that A1298C is the cause of stroke in an individual patient. Differences in genetic background, nutritional status, environmental exposures, study design, and other vascular risk factors may influence the observed associations. Moreover, the absence of C677T does not exclude other causes of hyperhomocysteinemia.

The American College of Medical Genetics and Genomics has emphasized that common MTHFR polymorphism testing has limited clinical utility in routine thrombophilia evaluation [7]. In this case, the genotype should therefore be considered an associated finding whose significance requires cautious interpretation, rather than proof of a hereditary thrombophilic disorder or a direct causal explanation for the infarction.

3.4. Negative F5 Leiden and F2 G20210A Results

Testing for factor V Leiden and the prothrombin G20210A variant was negative. These results exclude the two specific genetic variants assessed but do not exclude every inherited or acquired cause of thrombosis.

The distinction is important because a negative genetic thrombophilia panel cannot independently establish that the stroke was caused by hyperhomocysteinemia or an MTHFR variant. The results must be interpreted alongside the clinical presentation, vascular imaging, cardiac assessment, and other laboratory findings.

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In this patient, the negative F5 and F2 results contribute to the overall etiological assessment but do not establish a specific alternative mechanism.

3.5. Collateral Circulation and Hemorrhagic Transformation

Collateral vascular circulation may represent a compensatory mechanism that helps preserve perfusion downstream of an arterial stenosis or occlusion. Depending on the vascular anatomy and imaging characteristics, it may suggest the involvement of pre-existing vascular adaptation. However, collateral circulation alone cannot determine the timing or cause of an arterial abnormality.

Similarly, petechial hemorrhagic transformation is a recognized imaging feature of ischemic infarction. Its occurrence may be influenced by infarct characteristics, reperfusion, and other clinical factors. It should not be interpreted as direct evidence of an MTHFR-related hypercoagulable state.

In this case, the collateral circulation and petechial hemorrhagic transformation should be described as radiological findings accompanying the cerebellar infarction. Their relationship, if any, to the metabolic and genetic abnormalities cannot be established from the available evidence.

3.6. Clinical Implications and Secondary Prevention

The management of hyperhomocysteinemia should focus on identifying and correcting reversible causes when present. If folate or vitamin B12 deficiency is documented, appropriate replacement may be indicated. Assessment of renal function and other relevant metabolic factors can also help guide management.

However, reducing homocysteine concentrations should not automatically be equated with effective secondary stroke prevention. The Vitamin Intervention for Stroke Prevention (VISP) trial did not demonstrate a significant reduction in its primary clinical outcome with the vitamin regimen studied [8]. The VITATOPS trial likewise did not establish a significant reduction in recurrent vascular events sufficient to support routine B-vitamin supplementation for all patients following stroke or transient ischemic attack [9].

The American Heart Association/American Stroke Association guideline on secondary stroke prevention does not recommend folate, vitamin B6, and vitamin B12 supplementation solely for the purpose of preventing recurrent stroke in patients with hyperhomocysteinemia [1]. This does not preclude treating a documented vitamin deficiency or another identified metabolic disorder.

Secondary prevention should be individualized according to the stroke mechanism and the patient's clinical characteristics, including appropriate antithrombotic therapy, assessment and management of vascular risk factors, and further investigation when clinically indicated. The presence of an MTHFR variant should not replace this established approach.

3.7. Limitations

This report has the limitations inherent in a single-patient observation. It cannot establish a causal relationship between homozygous MTHFR A1298C, hyperhomocysteinemia, and ischemic stroke.

The interpretation is also limited by the absence, in the information currently available for this manuscript, of the exact plasma homocysteine concentration, folate and vitamin B12 concentrations, and detailed renal function results. These values should be added if they were measured. The exact genetic nomenclature should also be confirmed against the original laboratory report.

Finally, the negative etiological investigations reduce the likelihood of the specific causes assessed but do not exclude every possible mechanism. Further clinical follow-up and additional results, where available, would help clarify the metabolic findings and subsequent clinical course.

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4. CONCLUSION

This case illustrates the diagnostic challenges of ischemic stroke in young adults when the initial etiological investigation does not identify a definitive conventional cause. The coexistence of hyperhomocysteinemia and homozygosity for the MTHFR A1298C variant, in the absence of the C677T, factor V Leiden, and prothrombin G20210A variants, raises questions about the potential contribution of homocysteine metabolism to the cerebrovascular event.

Nevertheless, the available evidence does not establish that the A1298C variant caused the hyperhomocysteinemia or the stroke. The assessment of potentially reversible metabolic abnormalities, including vitamin deficiencies and impaired renal function, may help guide individualized management. Secondary prevention should remain based on established recommendations and the patient's overall clinical profile. Further studies are needed to clarify the clinical significance of MTHFR A1298C in ischemic stroke and to identify the circumstances in which genetic and metabolic findings may meaningfully influence clinical care.

REFERENCES

1. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021;52(7):e364–e467. doi:10.1161/STR.0000000000000375.
2. Putaala J. Ischemic stroke in young adults. Continuum (MinneapMinn). 2020;26(2):386–414. doi:10.1212/CON.0000000000000833.
3. Kelly PJ, Rosand J, Kistler JP, Shih VE, Silveira S, Plomaritoglou A, et al. Homocysteine, MTHFR 677C→T polymorphism, and risk of ischemic stroke: results of a meta-analysis. Neurology. 2002;59(4):529–536. doi:10.1212/WNL.59.4.529.
4. Hankey GJ, Eikelboom JW. Homocysteine and stroke. Lancet. 2005;365(9455):194–196. doi:10.1016/S0140-6736(05)17751-4.
5. Kumar A, Sharma R, Misra S, Nath M, Kumar P. Relationship between methylenetetrahydrofolate reductase (MTHFR) gene (A1298C) polymorphism with the risk of stroke: A systematic review and meta-analysis. Neurol Res. 2020;42(11):913–922. doi:10.1080/01616412.2020.1798107.
6. Dong X, Wang J, Wang G, Wang J, Wang L, Du Y. MTHFR A1298C gene polymorphism on stroke risk: an updated meta-analysis. Genes Environ. 2021;43:40. doi:10.1186/s41021-021-00208-z.
7. Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Genet Med. 2013;15(2):153–156. doi:10.1038/gim.2012.165.
8. Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, et al. Lowering Homocysteine in Patients With Ischemic Stroke to Prevent Recurrent Stroke, Myocardial Infarction, and Death: The Vitamin Intervention for Stroke Prevention (VISP) Randomized Controlled Trial. JAMA. 2004;291(5):565–575. doi:10.1001/jama.291.5.565.
9. VITATOPS Trial Study Group. B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial. Lancet Neurol. 2010;9(9):855–865. doi:10.1016/S1474-4422(10)70187-3.
10. Boot E, Ekker MS, Putaala J, Kittner S, De Leeuw FE, Tuladhar AM. Ischaemic stroke in young adults: a global perspective. J NeurolNeurosurg Psychiatry. 2020;91(4):411–417. doi:10.1136/jnnp-2019-322424.
11. Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. Am J Epidemiol. 2000;151(9):862–877. doi:10.1093/oxfordjournals.aje.a010290.

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12. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ. 2002;325(7374):1202. doi:10.1136/bmj.325.7374.1202.

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