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Case Report

A deadly combination of the point mutation A1298C in the MTHFR gene, and the 4G/5G polymorphism in the PAI-1 gene of a young patient with a left MCA infarct. A case presentation and review of the literature

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Abbreviations CT: Computed Tomography; ED: Emergency Department; GCS: Glasgow Coma Scale; ICP: Intracranial Pressure; ICU: Intensive Care Unit; MCA: Middle Cerebral Artery; MRA: Magnetic Resonance Angiography; *MTHFR*: Methylene Tetrahydrofolate Reductase; NIHSS: National Institutes of Health Stroke Scale; OR: Operating Room; PAI-1: Plasminogen Activator Inhibitor-1; PbrO2: Partial Pressure of Oxygen in Brain tissue, PCR: Polymerase Chain Reaction; PCT: Procalcitonin; rtPA: Recombinant Tissue Plasminogen Activator; SECRETO: Searching for Explanations for Cryptogenic Stroke in the Young; TIA: Transient Ischemic Attack

Abstract

Background: Cerebral infarction is a potentially fatal pathological entity, which has been associated with numerous risk factors, such as family history of stroke, hypertension, dyslipidemia, diabetes mellitus, smoking and trauma. On the contrary, the role of prothrombotic gene polymorphisms as risk factors of stroke has not been yet fully established.

Case presentation: A 24-year old man with a thrombophilic profile sustained a left sided Middle Cerebral Artery (MCA) infarction. He was intubated due to his rapid clinical aggravation and underwent initially a left sided hemicraniectomy and soon after that a right sided hemicraniectomy without any significant response. He died due to severe sepsis in the ICU (Intensive Care Unit) the eleventh day after his admission. The laboratory exams showed that he was homozygote for the point mutation A1298C of the methylenetetrahydrofolate reductase (*MTHFR*) gene, and heterozygote for the 4G/5G polymorphism of the Plasminogen Activator Inhibitor-1 (PAI-1) gene.

Conclusions: Both mutations may have an association with the development of a stroke. Thus genetic testing could possibly assist physicians in prognosis and treatment strategizing of patients with stroke.

Introduction

Cerebral infarction is a pathological entity with high morbidity and mortality rates and is usually managed in specialized stroke or neuro-Intensive Care Units (ICUs). Different clinical and radiological findings have been proposed as predictor factors. National Institutes of Health Stroke Scale (NIHSS) score larger than 20 for dominant or 15 for non-dominant strokes, younger patients, and early hypodensityin more than half of the brain region supplied by the Middle Cerebral Artery (MCA) such as the basal ganglia and midline shift of more than 5 mm are some of the most used prediction criteria.

One less studied predisposing factor for MCA infracts are the gene mutations related to patient's thrombotic mechanism. These are specific genetic polymorphisms affecting the Plasminogen Activator Inhibitor 1 (PAI-1), the Methylenetetrahydrofolate Reductase gene (*MTHFR*), Factors II and V [1-6]. Impairment of thrombolysis mechanism has been linked to the pathogenesis of ischemic stroke in the past [7]. Fibrin clots are normally dissolved by plasmin which represents the major enzyme for the fibrinolysis. Plasminogen is converted to plasmin by tissue plasminogen activator (tPA) and in this event the inhibitor is Plasminogen Activator Inhibitor (PAI-1) [8]. Elevated concentration of PAI-1 in the plasma could be related to reduce fibrinolysis and subsequently to increased possibility for a thrombotic event [9].The 4G/5G polymorphism constitutes an insertion/deletion of a guanine nucleotide in the promoter region of the PAI-1 gene and is detected 675 base pairs away from the starting point of gene transcription [9]. This polymorphism is associated with elevated PAI-1 levels in human plasma as it increases about six times the production of mRNA in vitro [1,9,10]. Atherothrombosis and plaque formation is favored by high plasma levels of PAI-1 [1]. Another significant polymorphism is the A1298C in the Methylene tetrahydrofolate reductase (*MTHFR*) gene. In exon 7, at nucleotide 1298 of *MTHFR* gene a change of A to C results

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to substitution of Glutamate (Glu) to Alanine (Ala) amino acid in codon 429 of S-adenosylmethionine regulatory area of *MTHFR* gene [11]. This change reduces activity of *MTHFR* enzyme and also leads to hyperhomocysteinemia [12]. Increased plasma levels of homocysteine have been valued as an independent risk factor for ischemic stroke [13].

Our purpose is to present a rare case of a young patient who sustained a malignant left MCA infract and died eleven days after his admission at our Neuro-ICU without being responsive to any of our conservative and surgical treatment maneuvers. He was found to have a thrombophilic profile according to our lab results.

Case presentation

A twenty-four-year-old male was admitted at the emergency department of our hospital with lethargy, aphasia, right hemiplegia, vomiting and loss of urine and feces within the previous 6 hours. He did not have any prior medical history, other than a benign cardiac murmur during childhood. He did not have anisocoria and his presenting Glasgow Coma Scale (GCS) at the Emergency Department (ED) was 10/15. The performed emergency Computer Tomographic (CT) scan revealed only edema in his left parietal cortex implying the initiation of ischemia in this affected region of the brain. Brain Magnetic Resonance Angiographic Imaging (MRA) indicated the presence of a left MCA infarct. His chest X-ray was indicative of aspiration. He was admitted to our ICU because of his initial crucial neurological presentation. He was not eligible for thrombolysis with rtPA (Recombinant Tissue Plasminogen Activator) because he had overcome the critical time limit of the 4.5 hours after his symptoms initiation.

The third day after his admission he was intubated due to his rapid neurological deterioration (GCS: 8/15). The new brain CT scan showed the hemorrhagic conversion of the initial ischemic area, severe cerebral edema with pressure effects on the ventricular system and 12 mm right midline shift. He underwent a minimally invasive surgical procedure for the placement of the 3-lumen neuro-monitoring system, which included Intracranial Pressure (ICP), brain tissue oxygen, and micro-dialysis catheters (Figure 1). A culture of bronchial aspirate received the next day showed infection by multiple drug resistant Klebsiella Pneumoniae and the patient was placed on antibiotic treatment. Patient's Procalcitonin (PCT) level was 0,87 mcg/L. The fifth day after his admission PCT rose to 2,53 mcg/L.

At the eleventh day of his hospitalization the patient had pupillary dilation to 6/6 and rising ICP values to 22 mmHg for 20 mins. He underwent a left fronto-parieto-temporal hemicraniectomy while the preexisting neuromonitoring catheters on the left side were removed. A new set of neuromonitoring catheters was installed on the right side. The post-operative brain CT showed the same findings as before, with less shifting of the midline, bleeding around the catheter tips and pneumocephalus. His PCT was then 7,03 mcg/L. After a few hours the patient's intracranial pressure increased abruptly to 22mmHg, not responding to antiedema administration. Significant tension of the skin flap in the hemi-craniotomized area was also noted. The patient was taken again to the OR where he underwent a right sided decompressive craniectomy and placement of a ventricular drain. The post-operative brain CT scan showed improvement of the midline shift. Intraventricular hemorrhage was noted and the ventricular catheter was located in the frontal horn of the lateral ventricle.

Within the next few hours he became mydriatic, his ICP rose to 31 and the new brain CT showed an extensive hypodense area with hemorrhagic elements in the left and right frontal hemisphere and intraventricular bleeding (Figure 2). He had severe brain edema with elimination of the volume of the ventricles and midline shift. His ICP remained at values around 30 mmHg. His last PCT was 92,89 mcg/L. The patient continued to deteriorate and he eventually developed refractory septic shock and died.

During his hospitalization in the ICU patient's ICP had a mean value of 12,06 mmHg however it remained higher than 20 mmHg for approximately 40 hours despite aggressive treatment. His medianpartial pressure of oxygen in brain tissue (PbrO2) value was 26,92mmHg with a maximum of 48 and a minimum of 7mmHg. However the patient had PbrO2 less than 20mmHg for 29 hours during his hospitalization.

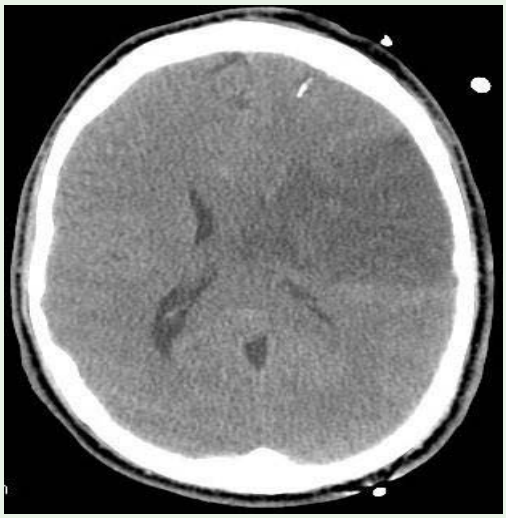

Figure 1: Axial non contrast CT image (5 mm) showing a left located MCA infarct.

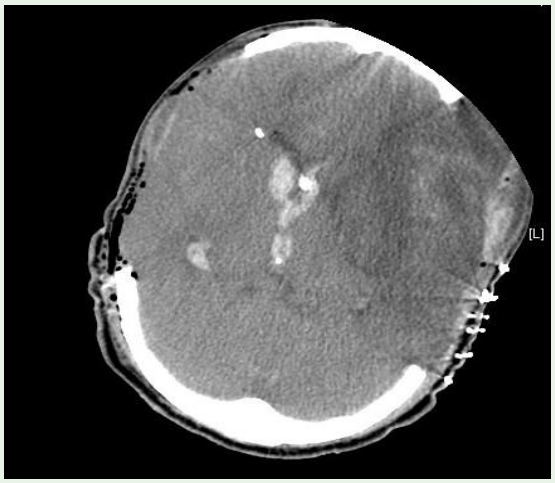

Figure 2: Axial non contrast CT image (5 mm) showing an extensive hypodense area with hemorrhagic elements in the left and right frontal hemisphere as well as intraventricular hemorrhage.

While, the patient was hospitalized at ICU, a sample of his genomic DNA was obtained from his peripheral blood leukocytes by the use of a globally recognized DNA elicitation test (Qiagen, Valencia, CA, USA). Thrombophilia testing was conducted including the genetic mutations of factor V Leiden G1691A (FV Leiden), prothrombin G20210A (FII), plasminogen activator inhibitor-1 factor 5G/4G (PAI-1) and methylenetetrahydrofolate reductase C677T and/or A1298C (*MTHFR*) variations. A Polymerase Chain Reaction (PCR) and allele- specific hybridization test was used for the recognition of any existing mutation or polymorphism related to pro-thrombotic genes. According to DNA test results, our patient was found to be homozygous for *MTHFR* A1298C and heterozygous for PAI-1 4G/5G polymorphisms.

Discussion

Significant risk factors for the development of stroke in young patients are: family history of stroke, hypertension, dyslipidemia, diabetes mellitus, and smoking, use of illicit drugs (such as cocaine), migraine and intracranial artery stenosis [14-16]. Our patient did not have family history of stroke and his blood exams were normal. Also, he was not a smoker or a cocaine user and he followed a healthy way of life. He was treated initially conservatively and after his rapid aggravation he was intubated. Unfortunately, all our surgical manipulations were proved to be ineffective and the patient died due to severe sepsis.

In young patients with ischemic stroke we perform laboratory exams for gene mutations regarding thrombotic mechanism mediators. According to the results of the performed PCR, our patient was homozygote for the point mutation A1298C of the *MTHFR* gene and heterozygote for the 4G/5G polymorphism of the PAI-1 gene. Several studies tried to investigate if this kind of polymorphisms is linked to increased risk for a stroke incident. A recently published study supports that thrombophilia does not amplify the risk of an ischemic event with the exception of heterozygote patients for factor V Leiden who have an elevated risk of TIA/amaurosisfugax, and patients with persistent presence of lupus anticoagulant [17]. There are also some publications that have found weak correlations between these two specific mutations and the risk for ischemic stroke [3,5,8,18,19].

On the contrary, there are also many studies supporting the strong correlation between the risk for ischemic stroke and heterozygote carriers of the 4G/5G polymorphism in the PAI-1 gene [1,2,19-21]. Attia et al, in their meta-analyses, supported that there is a possible correlation between the 4G/5G polymorphism and the risk for an ischemic event [1]. They claimed that stroke heterogenicity and linkage disequilibrium between the PAI-1 polymorphism and another existing polymorphism could explain the wide spectrum of the reported results among the genetic studies for PAI-1 [1]. The correlation between 4G/5G polymorphism and the elevated risk for ischemic stroke was also found by the up to date meta-analyses of Cao et al, although it was only partly supported under the recessive and the allelic model [2]. Kucukarabaci et al, prospectively analyzed the DNA of 253 patients who sustained an acute ischemic cerebrovascular event in their effortto extract information about the association between 4G/5G polymorphism of the PAI-1 gene and activity of the PAI-1 enzyme [19]. They reached the conclusion that the co-existence of the 4G/5G polymorphism with low plasma PAI-1 levels is an indicator for elevated risk of stroke in their studied population [19]. Furthermore Ranellou et al, compared the existence of DNA mutations in young patients suffering from ischemic stroke to the existence of DNA mutations in healthy controls [20]. According to their results, the predominanceof 4G/5G polymorphism in the PAI-1 gene has been found elevated in young patients with an acute cerebrovascular event than in healthy subjects [20]. Similarly Wiklund et al, studied the risk of stroke in correlation with the presence of 4G/5G polymorphism of the PAI-1 gene in two different cohorts of patients [21]. He concluded that 4G/5G polymorphism, hypertension and diabetes are three independent predictor factors for ischemic stroke [21]. In the study of Bang et al, it was supported that patients with the 4G/5G polymorphism have an increased risk for an ischemic event [22].

The same correlation was also supported independently for the homozygote patients of A1298C thesis in the *MTHFR* gene [13,23-25]. In a recent prospective study (2015) conducted in Eastern Chinese Han population the authors evaluated the presence of *MTHFR* mutations in 199 patients with ischemic stroke and 241 healthy subjects [13]. The A1298C mutation was correlated significantly with stroke patients [13]. Interestingly, in another study performed in Turkish Caucasian population, the authors analyzed the genomes of 92 ischemic stroke patients, 28 hemorrhagic stroke patients and 259 healthy controls for the existence of *MTHFR* mutations [23]. They concluded that *MTHFR* mutations (C667T and A1298C) are independent risk factors for both hemorrhagic and ischemic stroke [23]. Likewise, in a prospective study conducted in Tunisia, the authors compared the observed mutations of *MTHFR* gene between 84 patients with ischemic stroke and 100 healthy subjects [25]. They concluded that presence of *MTHFR* C677T and A1298 polymorphisms (separately or in combination) are important risk factors for stroke [25]. At last, in their meta-analysis Zhang et al at studied the role of *MTHFR* mutations as a contributing factor in the genesis of stroke in adults [24]. They concluded that *MTHFR* A1298C mutation is a significant risk factor for stroke in adult patients and in addition its presence may have predictive value for a future incidence of stroke especially in Asian populations [24]. Our patient had both of these two mutations which are rarely documented in the literature. According to our opinion this was probably a significant contributing factor to his severe left MCA infraction.

Additionally, it should be mentioned that in a recent meta-analysis about the correlation between plasminogen activator inhibitor-1-675 4G/5G polymorphism and sepsis it was found that there is a significant increase in mortality rates among the carriers [26]. According to Madach K et al, the Caucasian patients who are bearers of the 4G allele of PAI-1 polymorphism have greater probability for multiple organ dysfunction syndrome and septic shock when they have sepsis related to pneumonia [27]. Furthermore, Menges T et al studied the impact of PAI-1 4G/5G mutation in severely injured patients and he concluded that it is also associated with high mortality rates [28]. So, the PAI 4G/5G polymorphism is correlated independently with elevated morbidity and mortality incidence in septic patients. Our patient was in sepsis which progressed rapidly as the value of PCT confirmed. In addition, hemicraniectomy is a severe form of trauma for every patient and consequently increases the mortality rates among patients with the PAI-1 4G/5G mutation.

Conclusions

In conclusion, the combination of PAI-1 4G/5G and *MTHFR*-A1298C mutations along with additional genetic and/or environmental factors might be liable for the high stroke risk and mortality among the carriers. The thrombophilic profile in young patients with stroke could be a significant predictor of the final outcome. Therefore, large prospective studies should be performed in order to extract safer conclusions about the validity of this examination. The SECRETO study (https://clinicaltrials.gov/ct2/show/NCT01934725) is one of them and is currently enrolling patients in an effort to give answers about the etiological factors of stroke among young people.

Authors' Contributions

Concept and design: Siasios I, Fotiadou A; Acquisition of data: Siasios I, Fotiadou A, Tsezou A, Papadopoulos D, Gatos C; Analysis and interpretation of data: all authors; Drafting the manuscript: Siasios I, Fotiadou A, Papadopoulos D; Critically revising the manuscript: all authors; Final approval of the manuscript: all authors.

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