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Case Report Open Access

A Rare Case of Saudi Girl with Recurrent Strokes and Abnormal Multiple Thrombophilia

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Abstract

Recurrent multiple symptomatic strokes are infrequent in paediatric population. The causes for such events are usually cardiac, multiple inherited thrombophilia; such as Protein C, Protein S, Antithrombin III, and Antiphospholipid Syndrome, and other causes. We report a case of Saudi Girl who presented in December 12, 2017 with right sided Hemiparesis. Central Nervous System (CNS) imaging revealed left sided ischemic infarction. Investigations showed that in fact she has multiple inherited thrombophilia risk factors. She was found to have homozygous mutations in Prothrombin Gene Complex FII (G20210A), a mutation in the gene encoding Plasminogen Activator Inhibitor-1. Heterozygous mutations in 2 Methylene Tetrahydrofolate Reductase (MTHFR): c.677C>T and c.1298A > c. She was also found to have high Lipoprotein A levels (656 mg/L) which is also a known risk factor for arterial ischemia specifically. We concluded that having multiple inherited Thrombophilia mutations can result in increased risk of severe and symptomatic Ischemic infarctions in children.

Keywords: Stroke; Ischemic infarction; Prothrombin gene mutation; Thrombophilia; Plasminogen activator inhibitor-1

Introduction

Thromboembolic events in children are not uncommon conditions. The majority of these events happen in the presence of certain risk factors. There are acquired and congenital risk factors. Among the congenital risk factors; certain mutations that affect specific genes involved in the synthesis of certain proteins that are involved in normal coagulation and hemostasis. There are physiological, naturally occurring anticoagulants that circulate in blood and their role is to maintain blood flow. Also some of them are involved in the fibrinolytic system. Defect in these mechanisms can lead to Cardiovascular Diseases (CVD) and Cerebrovascular Accidents (CVAs) that are considered to be the leading cause of death in adults. In Pediatric patients, it is very rare with an estimated incidence of about 1 per 100,000 per year [1].

There are many studies focused on the naturally occurring anticoagulants, hemostatic markers and also on prothrombin gene polymorphisms as risk factors for stroke. They are all involved in stroke pathogenesis in significant number children with strokes. They are responsible for stroke and other thromboembolic conditions in at least 10%-30% of all pediatric stroke patients [2].

Spontaneous unprovoked strokes have been reported in children with Prothrombin Gene mutations. FII G20210A allele within the 3'-untranslated region of the prothrombin (PT) gene. Also, mutations resulting in defects of the Methylene Tetrahydrofolate Reductase (MTHFR) molecule were found to be associated with spontaneously occurring childhood strokes [3]. Furthermore, an elevated level of lipoprotein (a) has been identified as a genetically determined risk factor for children with strokes beyond the neonatal period [4]. In addition, it has been found that patients suffering from deep venous thrombosis and in symptomatic childhood carriers of the FV G1691A gene mutation, risk of strokes is increased and has been linked to increased levels of plasminogen activator inhibitor-1which leads to diminished fibrinolytic function and activity [5,6].

Case Presentation

A 9-year-old girl came to emergency department on February 13, 2018 complaining of right hand weakness and loss of grip. She has similar attacks of sudden onset of weakness over last few months. No family history of thrombosis or stroke at a young age. She was admitted, and MRI brain was done. It has shown scattered left cerebral preventricular/subcortical white matter recent ischemic foci, representing ischemic infarction. She initially was started on Aspirin 5 mg per kilogram daily. Then she was started on Low Molecular Weight Heparin 1 mg /kg/day subcutaneously. Thrombophilia work up was initiated. It was found that she has homozygous mutation in the Prothrombin Gene Complex (G20210 G>A). She was also found to have a mutation in the gene coding for Plasminogen Activator Inhibitor-1 (genotype 4G/4G homozygous). Also she has mutations in the genes endoing for Methylene tetrahydrofolate reductase (MTHFR) (c.677c>T: genotype / T heterozygous) and (c.1298A >c: genotype A/C heterozygous).

Discussion

Stroke in children is not a rare phenomenon [7]. Krishnamurthi et al. [8] found that in 2013 alone; the prevalence of Paediatric Ischemic strokes (IS) was 97,792 (59.3%) and prevalence of haemorrhagic stroke (HS) was 67,621 (40.7%). There was an increase of 35% since 1990. Of all paediatric strokes, mortality was 19.9%, significant disability was present in 40% [8]. Ischemic stroke in children can occur as a result of mainly 3 etiologic categories: infections, congenital heart diseases, and inherited or acquired hyper coagulable conditions. Inherited

Hypercoagulable conditions (Inherited Thrombophilia) represent 10%-25% of all causes of ischemic strokes in children. Yet, approximately 30% of children with strokes have no identifiable established risk factors [9].

Congenital Hypercoagulable states can be divided into two types:

1. Deficiency of Direct Natural Anticoagulants (Like Protein C, Antithrombin)

2. Deficiency of Antifibrinolytics (Such as deficiency of Plasminogen Activator Inhibitor-2)

This patient has deficiency of both types. She has a Prothrombin Gene Mutation G20210A as well as Plasminogen Activator Inhibitor-1. Both of which are proven risk factors for the development of thromboembolic events. Among inherited thrombophilia, only homozygous Methylene Tetra-Hydrofolate Reductase (MTHFR) C677T Polymorphism has been shown to independently increase the risk of stroke [10]. However, combinations of multiple inherited thrombophilia can increase the risk of first and recurrent strokes in children. Prothrombin Gene Mutation G20210A is the second most common cause of inherited thrombophilia after Factor V Leiden. The carrier rate of FIIG20210A is about 3% of the general population. In a systematic review that looked at global prevalence of FII G20210, Dziadosz et al. [11] found that it varies from one to another and has a carrier rate of 15.2% in some societies [12]. In children, it has been found that FII G20210A is associated with 30% of Central Nervous System (CNS) events and 67% of all arterial events [11]. Unlike other causes of inherited thrombophilia, especially Factor V Leiden mutation, FII G20210A is associated more with arterial rather than venous thrombosis [13]. It has also been observed by De Stephano et al. [14] that heterozygous carriers of FII G20210A are at risk for recurrent thromboembolism. In a review of a cohort of patients with recurrent thromboembolism the conclusion was if FII G20210A carrier individuals experience more than one episode of thromebolic events then they should be started on anticoagulation to prevent complications [14].

There are two Plasminogen Activator Inhibitors in the fibrinolytic pathway. The first, Plasminogen activator inhibitor-1 which is a serine protease inhibitor (serpin) that inhibits Tissue plasminogen Activator (tPA) and Urokinase (also known as Urokinase-Type Plasminogen Activator uPA). Deficiency of PIA-1 actually leads to increase risk of bleeding because of the increased levels of activation of plasminogen to plasmin which will lead to excessive fibrinolysis [15]. On the other hand, increased levels of PIA-1 leads to increased risk of thrombosis [16]. There are other roles of PIA-1 in the process of vascular inflammation, atherosclerosis, and myocardial infarction [17]. PIA-1 gene is located on chromosome 7q21.3 [18]. There are different polymorphisms of PIA-1. The most common is 4G/5G polymorphism in the promoter region. 4G/5G polymorphism is associated with increased PPAI-1 activity and increased risk of thrombosis risk. Initial studies failed to find a strong association between PAI-1 4G/5G polymorphism and stroke [19]. However, further and subsequent studies showed that, although not as an independent risk factor for stroke, PAI-1 4G/5G polymorphism can cause a stroke when associated with other risk factors [20]. Plasminogen Activator Inhibitor-2 (PIA-2) is a 393-amino acid protein that functions as an inhibitor of both tPA and uPA [21]. The gene encoding PIA-2 is on chromosome 18q21-23 [22].

There was also an increased level of Lipoprotein-a in this patient. Lp(a), an atherogenic, hypofibrinolytic, cholesterol-carrying lipoprotein. Studies have shown that in homozygous Plasminogen Activator Inhibitor-1 4G/5G Polymorphism; levels of Lipoprotein (a) are increased. Levels greater than 30 mg/dl are associated with atherosclerosis risk as well as ischemic strokes [23].

The heterozygosity for the Methylene Tetrahydrofolate Reductase (MTHFR) gene (C677T and A1298C) does not represent any risk for stroke. In fact, even homozygous MTHFR is not enough to initiate a stroke or first thromboembolic event in patients without presence of other risk factors [24]. The more common variant MTHFR C677T is found in as much as 61% of the population in some studies [25].

Conclusion

Presence of 4G/5G PAI-1 polymorphism, Prothrombin Gene Mutation (FII G20210A, as well as elevated Lipoprotein-a levels present a significant risk factors for first and subsequent strokes. This is probably the first case in children with all these 3 risk factors combined which justified anticoagulation therapy for life.

What is the evidence for management of patients with combined thrombophilia? How long would you treat? There is no consensus on duration of therapy. Several factors are to be considered when making a decision regarding initiation and duration of anticoagulation therapy; such as age, family history, site, severity of thromboembolic event. If the risk of recurrence is high; the suggestions are to continue for at least 2 years from the last event [26].

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