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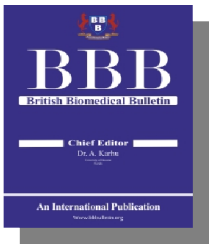

Case Report

Interplay of Genetic Factors Leading to Stroke in a Child with Down's Syndrome - A Rare Case Report

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A R T I C L E I N F O

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A B S T R A C T

Stroke has emerged as an important cause of acquired brain injury in newborns and children. Genetic factors contribute significantly for stroke in young. We report a 2 year old female child with Down's syndrome with left sided hemiparesis. On investigating MTHFR gene mutation (homozygous wild status at 677 and 1298 positions of MTHFR gene) and Protein S deficiency both were detected in the child. As plasma homocysteine levels were normal, so cause of stroke of being a protein S deficiency or MTHFR gene, as an isolated risk factor for stroke or interplay both of genetic factors was considered. **Conclusion:** This case marks the importance of coexistence of one or more risk factor in the occurrence of stroke in young and also identification of those risk factors at the earliest may help in improving overall outcome.

Case Report

A two year old female child with Down's syndrome presented to us with of sudden onset of left sided weakness with facial palsy. In view of sudden onset of neurological deficits, stroke in young was considered. The child had no significant past history. Parents of the child were evaluated for MTHFR gene mutation and were found to have carrying CC and AA genotypes, suggesting the homozygous wild status at 677 and 1298 positions of MTHFR gene (In view of the child being DOWN'S syndrome, parents were evaluated). But the child was not evaluated. There was no history of stroke in family members. Birth history was not significant.

On examination child had left sided hemiparesis with facial weakness. The child had features of Down syndrome. There were no meningeal signs, nor signs of raised intracranial tension. There were no neurocutaneous markers.

Investigations revealed anaemia with Hb of 8gm%, platelets were normal. Serum electrolytes, blood sugar, serum lipids were normal, except mild elevation of triglycerides was normal. PT and aPTT, LFT, CSF analysis was normal. Tuberculosis work up was negative. Serum Homocysteine was also normal. ANA was negative. Protein C was normal, but Protein S was significantly low.

MRI brain along with Angiography revealed diffuse right temporo-parietal infarct with thrombus in the right middle cerebral artery. As parents were positive for MTHFR gene mutation, we evaluated the child. Surprisingly was also carrying homozygous wild status in 677 and 1298position of MTHFR gene (PCR was performed using the flaking primer for the SNPs 677C>T and 1298A>C in MTHFR gene and PCR products were digested to completion using Hinfl and Mboll enzymes respectively).

The child was diagnosed to have both MTHFR gene mutation and congenital Protein S deficiency. A mutation in MTHFR gene was considered as an isolated risk factor for stroke along with Protein S deficiency. The child was treated with heparin for five days and then with oral aspirin. The child recovered slowly with gradual improvement in power and was discharged with long term prophylaxis of aspirin and counselling about future risk. Parents were also advised to get screened for Protein S deficiency and counselled about the disease as they also carried MTHFR gene mutation and are potential candidates for stroke.

Discussion

Stroke has emerged as an important cause of acquired brain injury in newborns and children. The ischemic varieties of arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are more common than brain malignancy (incidence ~5/100,000/yr.) and affect 1 in 2,000 newborns. A similar number suffers from hemorrhagic stroke (HS) and other forms of cerebrovascular disease. In children the diagnosis of stroke is frequently delayed or missed. This is due to subtle and nonspecific clinical presentations, and a lack of awareness by primary care pediatric physicians. The acute onset of a focal neurologic deficit in a child is stroke until proven otherwise. The most common focal presentation is hemiparesis but acute visual, speech, sensory, or balance deficits also occur. Children with these presentations require urgent neuroimaging and consultation with a child neurologist as emergency interventions may be indicated.[1]

Stroke is a multi-factorial polygenic, complex disease resulting from the combination of vascular, environmental and genetic factors.[2] There is a large body of

evidence, suggesting a genetic component to stroke. Animal model studies, twin and family-based association studies have suggested the substantial genetic component of stroke. Studies from the different ethnic regions of the world have reported variable results in the association of Apolipoprotein E (APOE), Methylenetetrahydrofolate reductase (MTHFR), Endothelial Nitric Oxide Synthase (ENOS), Factor V Leiden (F5), Cytochrome P450 4F2 (CYP4F2), beta-fibrinogen and Phosphodiesterase 4D (PDE4D) gene in stroke. There has been substantial evidence from the European descent genetic studies showing that genetic risk of stroke varies as per specific subtypes of ischemic stroke.[3] Prothrombotic disorders (protein C and protein S) have been receiving special attention during the past decade, because thromboembolic events are a major cause of AIS in children. [4]

Prevalence of MTHFR C677T mutation differs in various populations, decreasing from East to West. The highest prevalence has been reported in Japanese population (59.8%), and it decreases toward western parts of Asia and Europe.[5] A common polymorphism (677C3T) in the gene encoding the N5, N10-methylenetetra-hydrofolate reductase (MTHFR) enzyme, which converts dietary folate to its active cofactor in Homocysteine catabolism, has been studied as a candidate genetic risk factor for stroke.[6] MTHFR acts at a critical metabolic juncture in the regulation of cellular methylation reactions, catalysing the conversion of 5, 10-methylenetetra-hydrofolate to 5-methyltetrahydrofolate, the methyl donor for the remethylation of homocysteine to methionine . The C to T transition mutation at position 677 within the MTHFR gene (677C-T) causes an alanine to valine substitution in the MTHFR protein and reduced enzyme activity.[7] Relative to the normal C/C genotype, the specific activity of MTHFR is reduced <35% with the heterozygous C/T genotype and <70% with the homozygous T/T genotype. This reaction is important for the synthesis of S-adenosylmethionine (SAM), the major intracellular methyl donor for DNA, protein, and lipid methylation reactions. Reduced MTHFR activity results in an increased requirement for folic acid to maintain normal homocysteine remethylation to methionine. In the absence of sufficient folic acid, intracellular homocysteine accumulates, methionine resynthesis is reduced, and essential methylation reactions are compromised. An increase in homocysteine and a decrease in methionine results in a decreased ratio of SAM to S-adenosylhomocysteine (SAH), which has been associated with DNA hypo methylation. (Risk factor for occurrence of Downs, as parents carried the mutation).[8]

Protein S is an antithrombotic plasma protein that serves as a cofactor of activated protein C anticoagulant activity.[9] Hereditary protein S deficiency is an autosomal dominant disorder, which was described in 1984 in several kindreds with low level of protein S and a striking history of recurrent thrombosis.[10] There was reported about 10% in families with inherited thrombophilia.[11,12] The most common non genetic cause of protein S deficiency is inflammatory illnesses, which activates the complement system. It leads to increase binding of protein S to C4b and causes free protein S deficiency.[13] Major manifestation of protein S deficiency is deep venous thrombosis, superficial thrombo-phlebitis, and pulmonary emboli. Ischemic stroke has been reported as a rare manifestation of protein S deficiency. The congenital deficiency of protein S is associated increased risk of juvenile arterial and venous thromboembolism.[14,15]

This case, though had the MTHFR gene mutation, but the level of homocysteine was normal. But child had

significantly low level of free protein S levels, which was the risk factor for stroke. The child had two genetic risk factors for stroke. MTHFR gene mutation is a known risk factor for stroke in young, and so as low levels of protein S. The contribution of each factor leading to stroke in this child is debatable, so as the recurrence of stroke. Normal levels of plasma homocysteine puts us in a dilemma. So the interplay of genetic factors was considered.

Conclusion

Stroke has emerged as an important cause of acquired brain injury in newborns and children. The ischemic varieties of arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are more common. Genetic factors play a major role in the occurrence of stroke in young. [1] MTHFR gene mutation should be considered as a cause of stroke, especially in Down's syndrome. Protein C and protein S should be routinely considered, as early detection will help the child when put long term prophylaxis.

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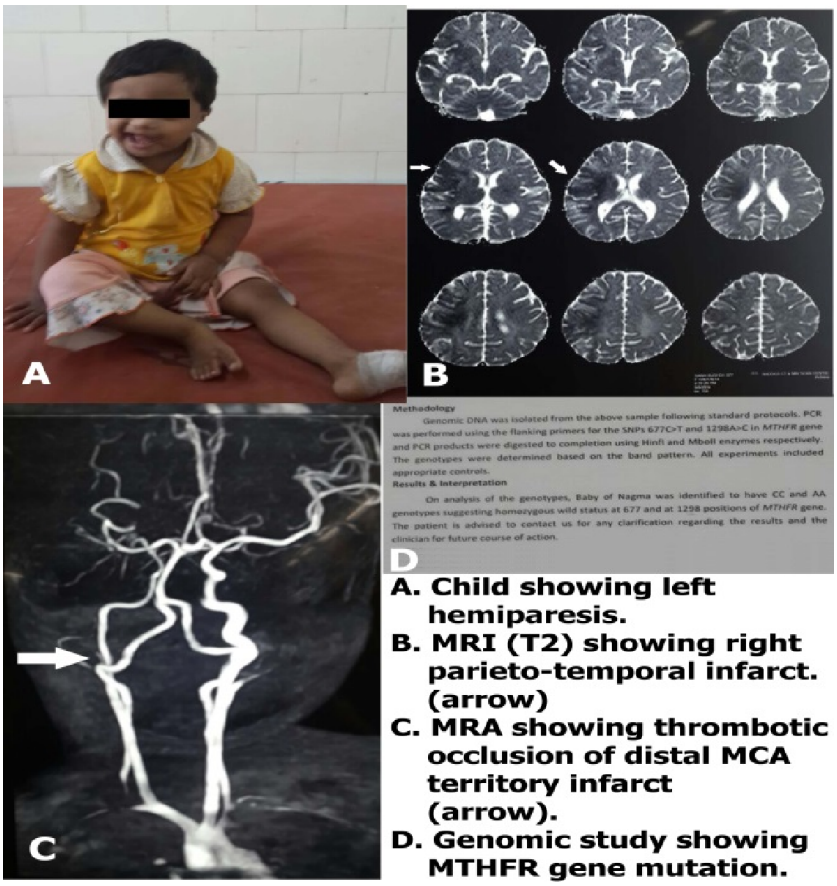

Figure 1. A,B,C,D (original pictures)