INTRODUCTION

Upshaw-Schulman Syndrome (USS) is an extremely rare hereditary disorder in which there is a severe deficiency of A Disintegrin And Metalloprotease with Thrombospondin repeats 13 (ADAMTS13) resulting in congenital Thrombotic Thrombocytopenic Purpura (TTP). It is a form of microangiopathic hemolytic anaemia characterized by pentad of neurological symptoms including renal abnormalities, thrombocytopenia, fever and Microangiopathic Hemolytic Anaemia (MAHA). The clinical signs are usually mild during childhood in patients with Upshaw-Schulman syndrome but may be associated with and aggravated in severe phenotype, often presenting with isolated and recurrent thrombocytopenia. Many times their symptoms are first noticed when they have infections or get pregnant.

This report describes a teen age girl presenting with renal and neurologic symptoms finally diagnosed USS.

CASE REPORT

A 13 years girl presented in the Emergency of Jinnah Hospital with complaint of sudden onset fits for 2 days. There was history of right sided weakness of the whole body. Past history revealed repeated episodes of similar complaints since early childhood. On the basis of history, physical examination and extensive investigations, patient was diagnosed as Upshaw-Schulman syndrome, a rare case of congenital Thrombotic Thrombocytopenic Purpura (TTP). She is now in remission and being maintained on twice weekly transfusions of Fresh Frozen Plasma (FFP).

ABSTRACT

A 13 years girl presented with history of sudden onset fits, altered sensorium and anuria for 2 days. There was also history of right sided weakness of the whole body. Past history revealed repeated episodes of similar complaints since early childhood. On the basis of history, physical examination and extensive investigations, patient was diagnosed as Upshaw-Schulman syndrome, a rare case of congenital Thrombotic Thrombocytopenic Purpura (TTP). She is now in remission and being maintained on twice weekly transfusions of Fresh Frozen Plasma (FFP).


INTRODUCTION

Upshaw-Schulman Syndrome (USS) is an extremely rare hereditary disorder in which there is a severe deficiency of A Disintegrin And Metalloprotease with Thrombospondin repeats 13 (ADAMTS13) resulting in congenital Thrombotic Thrombocytopenic Purpura (TTP). It is a form of microangiopathic hemolytic anaemia characterized by pentad of neurological symptoms including renal abnormalities, thrombocytopenia, fever and Microangiopathic Hemolytic Anaemia (MAHA). The clinical signs are usually mild during childhood in patients with Upshaw-Schulman syndrome but may be associated with and aggravated in severe phenotype, often presenting with isolated and recurrent thrombocytopenia. Many times their symptoms are first noticed when they have infections or get pregnant.

This report describes a teen age girl presenting with renal and neurologic symptoms finally diagnosed USS.

CASE REPORT

A 13 years girl presented in the Emergency of Jinnah Hospital with complaint of sudden onset fits for 2 hours. There was history of right sided weakness as well. Patient had a history of similar episodes in the past, but the present episode was more severe. Past history also included repeated admissions in hospitals with complaint of altered sensorium, jaundice and anuria. Her parents were first cousins. She had 3 siblings and none of them ever had such complaints and all were healthy.

She had undergone splenectomy in another hospital 2 months back with the suspicion of immune-mediated platelet destruction.

At the time of admission in Emergency her hemoglobin (Hb) was 4.8 g/dl, Total Leucocyte Count (TLC) was 28.4 x 10^9/l, with 90% neutrophils and platelets were 40 x 10^9/L; PT was 12/12 seconds and APTT was 31/30 seconds. Peripheral smear revealed numerous fragmented RBCs and few nucleated red cells. Bilirubin was raised (4.5 mg/dl) with unconjugated hyperbilirubinemia. Blood Urea Nitrogen (BUN) (104 mg/dl), and creatinine (2 mg/dl) levels were also elevated. LDH level was 2230 U/L (normal = 225 - 450U/L). Direct Coomb’s test was negative. Blood cultures revealed no growth. She was diagnosed as a suspected case of microangiopathic hemolytic anaemia on the basis of history, physical examination findings and peripheral smear examination which revealed schistocytes on repeated occasions.

She was treated with plasma infusions and later with plasmapheresis followed by immunosuppression in the form of inj Solumedrol 1g intravenously X OD for 3 days. Her CT scan of brain was done in order to find out the cause of her right sided weakness. It revealed an old infarct in right parietal region and hemorrhagic infarcts in right frontoparietal region. There were hemorrhagic infarcts in left frontoparietal region as well with mild cerebral atrophy. Her Hb improved to 8.7 g/dl and platelet count increased to 170 x 10^9/L after one week. LDH reduced to 900 U/L. Neurological symptoms recovered partially.

Due to her history of such repeated episodes since childhood her ADAMTS13 levels were done, which were markedly low 300 ng/ml (630 - 850 ng/ml). Patient was finally diagnosed as a confirmed case of Upshaw-Schulman syndrome. As these patients do not benefit from immunosuppressant therapy, thus immunosuppressive agents were discontinued. Plasmapheresis was also discontinued as it is not required in this
 syndrome because there is no autoantibody against ADAMTS13. Her condition improved and now she is being maintained on fresh frozen plasma infusion twice weekly. She is now on follow-up with CBC and LDH.

**DISCUSSION**

The diagnosis of this rare disorder is extremely important as these children are often misdiagnosed as ITP and treated with immunosuppression which is of no benefit and may even result in serious consequences. This patient was also initially misdiagnosed and managed as a case of immune thrombocytopenia, repeatedly, had received immunosuppression and had even undergone splenectomy. The classical hallmarks of USS are severe neonatal jaundice with a negative direct Coomb's test. There are repeated childhood episodes of thrombocytopenia and MAHA that are reversed by infusions of Fresh Frozen Plasma (FFP). Often only an isolated thrombocytopenia occurs, causing physicians to sometimes overlook this important disease. Although this patient did not present with neonatal jaundice but recurrent episodes of MAHA and neurological symptoms were present since early childhood. USS is an extremely rare disease, and to date, it is estimated that there have been only about 100 patients worldwide. Nara Medical University has functioned as a TMA referral centre in Japan since 1998 and collected a large dataset of 919 patients with TMA between 1998 and 2008. In this registry, only 41 USS patients in 36 different families were identified who ranged in age from early childhood to 79 years of age. Only one case report is published in Pakistan recently.

ADAMTS13 deficiency is prothrombotic, but this alone is unable to precipitate acute symptoms. Thus, second hits or triggering factors should exist. In this patient recent episode of MAHA was precipitated by upper respiratory tract infection. There are two clinical phenotypes of USS, termed as the early-onset and the late onset phenotypes.

The phenotype of the homozygous p.R193W/p.R193W mutation is mild and the patients carrying this mutation usually have mild thrombocytopenia during childhood unless they are exposed to provoking stimuli, such as a cytokine storm during influenza virus infection. However, after adolescence the gender disparity apparently determines the ultimate outcome of these USS-patients, as adult females have more episodes of TTP than males. Although gene analysis was not done in this case but phenotypically she had a severe presentation.

Pregnancy undoubtedly is a strong inducer of overt TTP in female USS-patients, although the pathogenesis is not fully known. However, it is now well established that plasma Von Willebrand Factor (VWF) levels remarkably increase as gestation progresses, alongwith the appearance of ultra large Von Willebrand factor multimers (UL-VWFMs), which are accompanied by reduced ADAMTS13 activity due to consumption, even in normal pregnant women. Thus, in pregnant USS women, an enormous excess of the substrate (larger VWF) relative to the ADAMTS13 enzyme is the most plausible pathogenic mechanism. Along with it, aging, interferon therapy and heavily drinking alcohol are also considered to be additional disease aggravating factors for USS patients.

An assay for ADAMTS13 activity should be done as a routine test to make and/or exclude a diagnosis of USS, when physicians come across the patients with thrombocytopenia of unknown etiology, especially during childhood.

The distinction between congenital and acquired TTP is important as it helps us to provide information to patients regarding their diagnosis (i.e; Upshaw-Schulman syndrome versus acquired immune mediated disease) and its specific consequences. Secondly, it provides correct information for the future management of female patients during pregnancy or other health related issues which can precipitate an episode of MAHA. Moreover, it also helps in family screening of asymptomatic members of family as disease may be precipitated in those individuals during pregnancy or an episode of infection.

The most important aspect of this case report is the mode of presentation. Equally important is the neurological aspect of this case. These features point towards importance of genetic mutational analysis in such patients which may predict severity of congenital TTP. Gene mutation in such cases is not available in Pakistan up till now. To some extent we can emphasize multicentre study on rare families with Upshaw-Schulman syndrome for possible genetic mutations which can predict severity and possible neurological and renal damage if not treated aggressively with FFPs. Possibly in near future recombinant ADAMTS13 will become available and patients with severe phenotypes can be benefitted with this product.
REFERENCES


