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**Case Report**

# Post-splenectomy Posterior Reversible Encephalopathy Syndrome in a β-Thalassemia Major child with Evans Syndrome

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**ABSTRACT**

Patients with β-Thalassemia Major are at risk of alloimmunization and autoimmunization because they need regular multiple blood transfusions. Here we are reporting a case of an 8 years old male child, known case of β-thalassemia major, who developed autoimmune pancytopenia, known as Evans syndrome, and post-splenectomy neurological complication Posterior Reversible Encephalopathy Syndrome (PRES). Evans syndrome (ES) is a rare autoimmune disorder characterized by autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) with or without immune neutropenia. There is no established evidence-based treatment. Steroids are used as a first-line therapy. Intravenous immunoglobulin is used as a life-saving therapy in severe cases. Rituximab and splenectomy are used as a second-line therapy. PRES is linked with hypertension. Characteristic clinical features of PRES are headache, blurring of vision, seizures, altered consciousness, cortical blindness or transient motor deficit.

**Keywords**: Autoimmune hemolytic anemia, Autoimmune thrombocytopenia, Autoimmune neutropenia, Evans syndrome, Posterior Reversible Encephalopathy Syndrome

## INTRODUCTION

β-Thalassemia Major is a hereditary hemolytic anemia. Patients with β-Thalassemia Major require life-long regular blood transfusions. They are at risk of developing anti-red blood cell antibodies (both allo-and autoantibodies). When autoantibodies are present against two or more blood cells it is known as Evan syndrome (ES). ES is an autoimmune disorder presenting with autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) with or without immune neutropenia with positive direct anti-human globulin test (DAT). ES is classified as primary (idiopathic) or secondary (associated with underlying disorder e.g., systemic lupus erythematosus, chronic lymphocytic leukemia, viral infections as HIV, following hematopoietic cell transplantation or repeated blood transfusions).[1] Exact etiology and pathological mechanism is unclear, but genetic and environmental factors contribute to disturbance of immune regulation. ES is a diagnosis of exclusion. Steroids and intravenous immunoglobulins are used as first-line therapy. Rituximab and splenectomy are used as second-line therapy. Various immunosuppressive drugs are used, if patient does not respond to second line therapy.[2,3] Here we are reporting a case of a child with β-Thalassemia Major with secondary Evans syndrome, who developed post-splenectomy PRES. Inadequate pain management in post-operative period leads to transient hypertension. Hypertension leads to Posterior Reversible Encephalopathy Syndrome (PRES). It is a reversible neurological sequela, but if left untreated, can lead to permanent brain damage.

## Case History

An 8 years old male child, a known case of beta thalassemia major, was admitted to our hospital for splenectomy and blood transfusion. Patient was vaccinated one month before against S. pneumoniae, N. meningitides and H. influenzae type B. On physical examination, patient had hemolytic facies, severe pallor, jaundice, tachycardia, tachypnea, hepatosplenomegaly (liver 6 cm and spleen 15 cm below costal margin in midclavicular line) at the time of admission (Figures 1 & 2).

**Figure-1:** Characteristic hemolytic facies (depressed nasal bridge, large cheekbones, protruding maxilla and teeth)

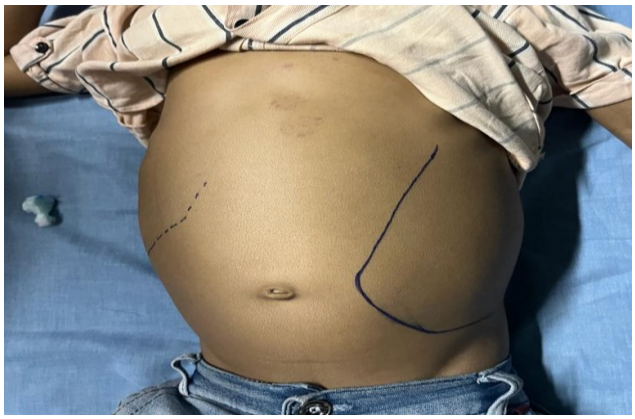
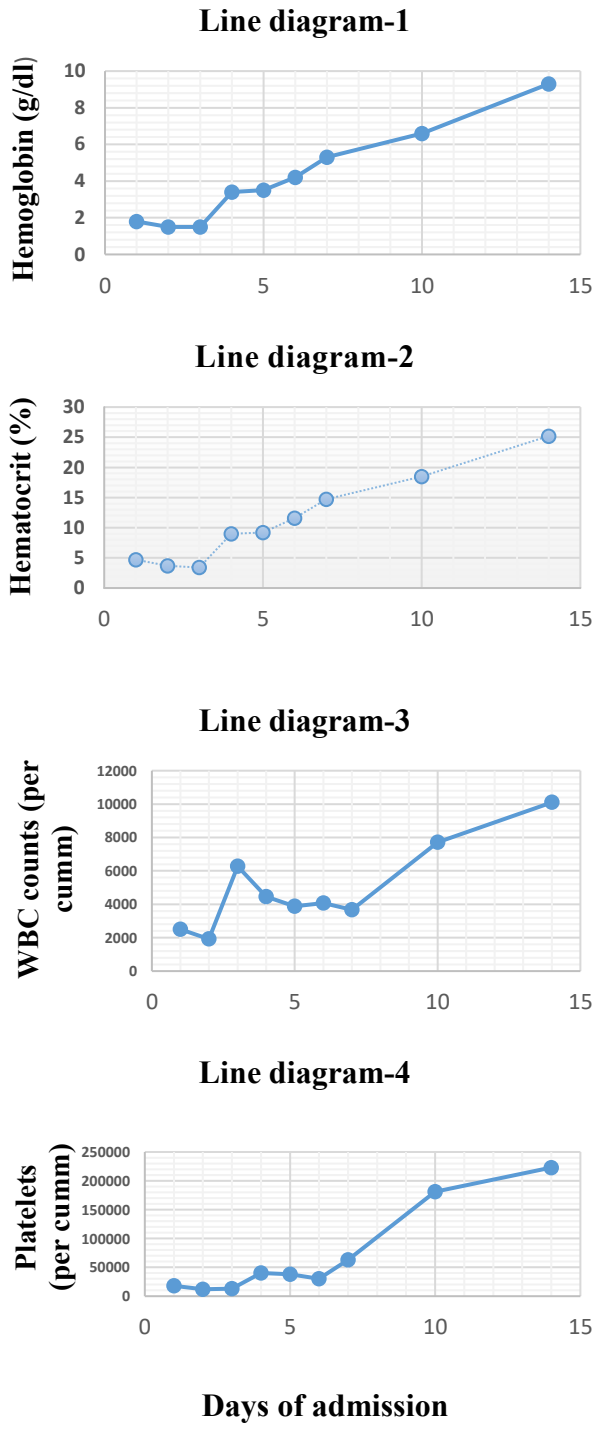


**Figure-2:** Surface marking for hepatomegaly (dotted line) and splenomegaly (continuous line)

Child had severe pancytopenia with Hemoglobin 1.8 gm/dL, hematocrit 4.7 %, RBC counts 1.02 million/cumm, white blood cells count 2510/cumm, and platelet counts 18,000/cumm. Total serum bilirubin was 2.2 mg/dL, direct bilirubin 0.6 mg/dL, indirect bilirubin 1.6 mg/dL, serum ferritin 6220 ng/ml and reticulocyte count 10.8% at the time of admission. Two units of packed cell volume (PCV) transfusion was done at 12 hours interval on first day.

On second day, hemoglobin was 1.5 gm/dL, hematocrit level 3.7 %, white blood cells count 1920/cumm and platelet counts 12,000/cumm. Patient had dark cola colored urine on second day. He was further transfused with two units of PCV and one unit of random donor platelets (RDP). At the same time direct antiglobulin test (DAT) and indirect antiglobulin test (IAT) were sent, both were strongly positive. On the basis of clinical presentation and investigations, a diagnosis of autoimmune pancytopenia was made. Treatment with prednisolone 2 mg/kg/day was started. Intravenous immunoglobulin (IVIG) could not be given to patient because of financial issues. He was transfused with one unit of PCV on third day also. His hemoglobin, hematocrit, white blood cells and platelet counts were repeated on 3rd, 4th, 5th, 6th, 7th, 10th and 14th days of admission (Line diagrams: 1 to 4). Patient had responded well to prednisolone. On 14th day of admission, hemoglobin was 9.3 gm/dL, hematocrit level 25.2 %, white blood cells count 10,100/cumm and platelet counts 2,23,000/cumm but DAT and IAT both remained strongly positive.



Prednisolone was tapered slowly over next 1 week as child was posted for splenectomy on 22nd day of admission. One unit of packed cell volume (PCV) transfusion was done before splenectomy. Splenectomy was done under general anesthesia and specimen sent for histo-pathological examination (Figure-3). In spleen biopsy, iron deposits were seen by Prussian Blue Stain (Figure-4).

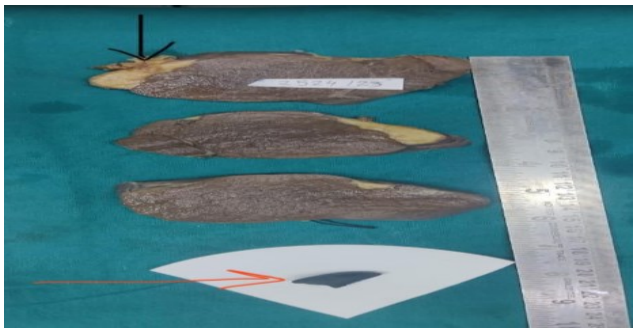


**Figure-3:** Splenic sections: black arrow shows splenic infarct. Red arrow shows Prussian blue stain positive splenic tissue

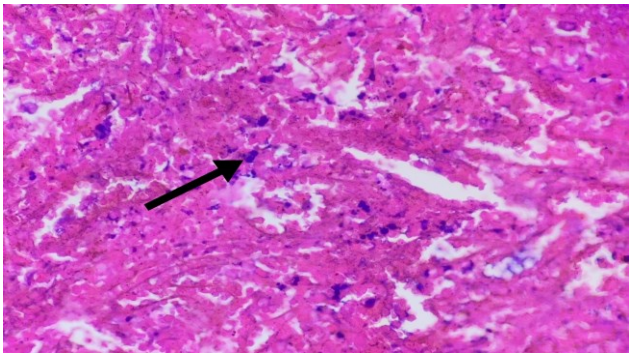


**Figure-4:** Prussian Blue Stain: black arrow showing positive for iron deposits in congested spleen (hemosiderosis)

Child was vitally stable during post-operative period. On third postoperative day negative suction drain was removed, following which child complained of severe pain at the drain removal site. Intravenous Paracetamol 15 mg/kg was given for pain relief but pain continued. Child had blood pressure < 90th percentile before drain removal. After severe pain, blood pressure was > 95th percentile (116/80). Child had continuous pain and severe occipital headache followed by blurring of vision. All symptoms worsened rapidly. After 1 hour blood pressure was > 99th percentile (142/86) and complete vision loss occurred. Child was not even able to see finger movements. Intravenous continuous infusion of Labetalol at the rate of 1 mg/kg/hour was started. CBC, serum electrolytes, blood sugar, serum creatinine were sent, all were within normal limit. Fundus examination was normal. MRI brain was done. MRI brain FLAIR image showed hyperintense lesions in bilateral parieto-occipital region (Figure-5A). MRI brain DWI images showed multiple areas of diffusion restrictions in bilateral temporo-occipital and cerebellar hemispheres (Figures-5B & 5C). All clinical and radiological features were suggestive of Posterior Reversible Encephalopathy Syndrome (PRES) as a neurological complication after splenectomy because of inadequate pain management in post-operative period or because of steroid treatment which was given for autoimmune pancytopenia.

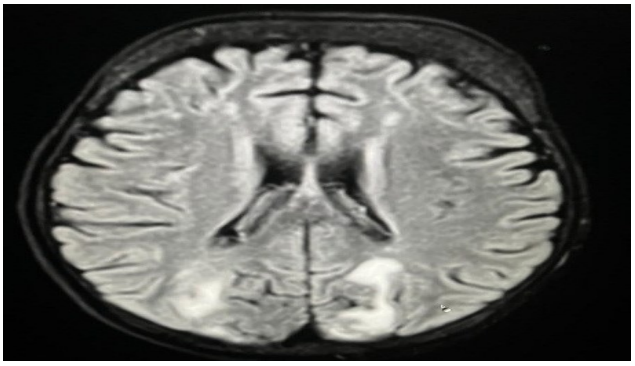


**Figure-5A:** MRI brain FLAIR image showing hyperintense lesions in bilateral parieto-occipital region

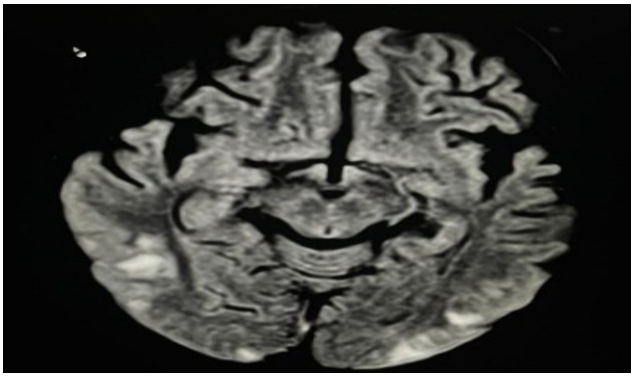


**Figure-5B:** MRI brain DWI image showing multiple areas of diffusion restrictions in temporo-occipital region

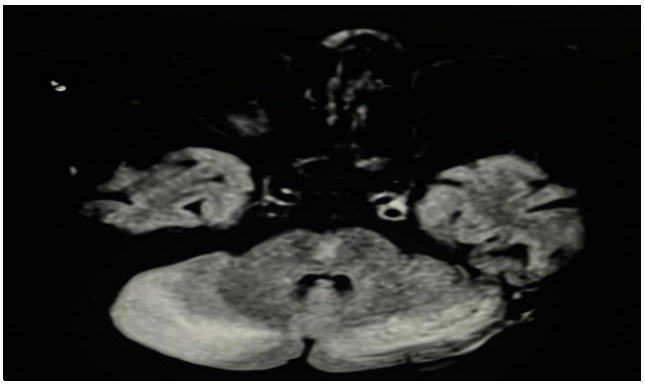


**Figure-5C:** MRI brain DWI image showing multiple areas of diffusion restrictions in cerebellar hemispheres

Within 24 hours of Labetalol infusion, BP was between 90th to 95th percentile, so Labetalol 0.5 mg/kg/hour intravenous continuous infusion was continued for next 12 hours, then tapered, stopped in next 12 hours. Tab Enalapril maleate 0.5 mg/kg/day was added orally.

On 6th postoperative day, BP was < 90th percentile, headache and visual symptoms resolved completely. Tab Enalapril maleate was tapered and stopped. CBC, DAT and IAT were also repeated. Hemoglobin was 8.2 gm/dL, hematocrit level 24.7 %, white blood cells count 9,003/cumm and platelet counts 3,22,000/cumm. DAT and IAT both were strongly positive. So, treatment with prednisolone at dose of 2 mg/kg/day was restarted. Oral iron chelators, Deferasirox (40 mg/kg/day) and Deferiprone (75 mg/kg/day), were continued. Patient was discharged after 36 days of admission. On follow-up, after one-week, neurological examination was totally normal, BP was normal. DAT and IAT were negative, so, prednisolone was tapered and stopped in next one week.

## DISCUSSION

Evans syndrome (ES) was first described by Robert Evans in 1951.[4] The diagnostic criteria for ES include presence of anemia, reticulocytosis, increased indirect bilirubin and fecal urobilinogen, presence of antibodies against RBC at 37º C, hemolysis of transfused RBC, presence of purpura and prolonged bleeding time. ES is a very rare chronic autoimmune disorder with reported incidence of 0.8-3.7 % patients with combined AIHA and ITP.[5]

ES is a diagnosis of exclusion. Exact etiology and pathological mechanism are unclear, but genetic and environmental factors contribute to disturbance of immune regulation. Recently, molecular theories explains that deficiencies of CTLA-4, LRBA, TPP2 and decrease CD4/CD8 ratio lead to ES. It is characterized by autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) with or without immune neutropenia with positive direct antiglobulin test (DAT). Steroids and intravenous Immunoglobulin are used as a first-line therapy. Rituximab and splenectomy are used as a second-line therapy. Various immunosuppressive drugs are used in patients who do not respond to second line therapy.[2] In severe and refractory cases, stem cell transplantation is only curative treatment.[6] Patients with autoantibodies may have higher transfusion rate and often require second line treatment with immunosuppressive drugs, splenectomy or alternative treatments.[7,8]

In our case, patient had severe autoimmune pancytopenia, and responded well to Prednisolone. Philip J et al reported a case of β-Thalassemia Major with alloimmunization and refractory autoimmunization treated with steroids followed by intravenous immunoglobulin (IVIG) and rituximab.[9] William V et al reported a case of 15 years old female with refractory AIHA and Thalassemia who responded with cyclosporine and prednisolone.[10] Our patient, after splenectomy, developed posterior reversible encephalopathy syndrome. PRES was first reported in 1996 by Hinchey.[11] PRES is a cerebrovascular syndrome, it is linked with severe hypertension that leads to disruption of brain autoregulation system, consequently resulting in endothelial dysfunction and reversible vasogenic oedema.[12] Vasogenic oedema occurs commonly within occipital and parietal regions relating to posterior cerebral artery supply. PRES is also linked with renal diseases, autoimmune disorders, immunosuppressant or cytotoxic drugs which lead to secondary hypertension.[13] PRES is a benign neurological condition but, if left untreated, permanent neurological damage can occur. The most common symptom of PRES is headache, followed by altered mental status, seizures, blurring of vision, cortical blindness, nausea/vomiting or transient focal neurological deficit.[3,14] In our patient, headache and blurring of vision were due to hypertension after splenectomy.

Rastogi A et al also reported a case of postoperative PRES in a 12 years old child suffering from thalassemia major with immune thrombocytopenia posted for splenectomy with an acute rise in blood pressure in the post-operative period.[15] Parikh NS et al reported in 99 cases, that steroid therapy frequently precedes the onset of PRES so there is temporal association between steroid exposure and PRES.[16] A diagnosis of PRES is usually made when patients have neurological symptoms, radiographic abnormalities and risk factors. MRI brain is the imaging modality of choice. High intensity signals in posterior region of brain suggest PRES. In our patient also MRI brain FLAIR and DWI images confirmed the diagnosis of PRES. Primary treatment for PRES is to treat underlying cause, pain management, reduction of blood pressure, and antiepileptics if required. Prognosis in most of PRES cases is favorable if treatment is started early.

## CONCLUSIONS

In β-Thalassemia Major patients, risk of allo- and autoantibodies against blood cells is high because they need regular multiple blood transfusions. Screening for alloimmunization and autoimmunization should be done regularly in such patients. Adequate pain management in post-operative period is crucial in pediatric patients, especially when patient is already on steroid therapy for autoimmune disorders, as these are the risk factors for PRES.

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