Thrombotic Thrombocytopenic Purpura in a Child with Diabetic Ketoacidosis

Abstract

Thrombotic thrombocytopenic purpura (TTP) secondary to diabetic ketoacidosis has been rarely reported and is considered as a rare complication. If left untreated, this condition could be life threatening with considerable morbidity and mortality. Herein, we report a 6-year-old girl with reduced consciousness and respiratory distress with a history of polydipsia and polyuria in the 2 weeks before hospitalization. The patient was initially diagnosed as diabetic ketoacidosis based on clinical and laboratory findings and treated accordingly. After treatment and during hospitalization although she had gained relative consciousness, she experienced seizure and reduced consciousness again. Considering laboratory and clinical findings and the patient’s underlying conditions (thrombocytopenia, renal failure, and high lactate dehydrogenase), TTP was suspected although ADAMTS13 test could not be done. Treatment with plasmapheresis was initiated, and after 48 h, the patient was conscious, and laboratory indices became normal within a few days. The patient was discharged after full recovery. TTP should be considered as a rare complication of diabetic ketoacidosis in patients with thrombocytopenia, renal failure, and reduced consciousness and should be immediately treated.

Keywords: Diabetic ketoacidosis, plasmapheresis, thrombotic thrombocytopenic purpura

Introduction

Thrombocytopenic purpura is a thrombocytopenic syndrome related to thrombocytopenic-associated multiorgan failure.[1] Thrombotic thrombocytopenic purpura (TTP) secondary to diabetic ketoacidosis has been rarely reported.[1] It is clinically defined as the beginning of thrombocytopenia and multiorgan failure such as renal failure and increased lactate dehydrogenase (LDH),[2] and it is considered as a rare complication.[1] The classic pentad of TTP includes fever, thrombocytopenia, microangiopathic hemolytic anemia, renal failure, and neurological symptoms. However, most patients do not experience all these five complications simultaneously, and TTP is suspected based on laboratory findings or by observing microangiopathic hemolytic anemia (on peripheral blood smear and observing red cell fragmentation) and thrombocytopenia.[4]

Early diagnosis of this disease is important because if it is not treated promptly, mortality rates increase to over 90%.[5] The most important laboratory findings include severe thrombocytopenia, hyperbilirubinemia, decreased hemoglobin rate, schistocytes and polychromasia, reticulocytosis, negative direct Coombs test, high LDH, high reticulocyte count, low haptoglobin, high creatinine in case of renal failure, normal coagulation test results, increased troponin T[4,5] in 50% of idiopathic TTP, normal hepatic test results, and/or reduced ADAMTS13 activity to <10%.[4]

The first measure to be taken for treatment is immediate daily plasmapheresis in cases of high clinical suspicion.[4] Plasmapheresis would replace ADAMTS13 and dispose antibodies.[5] Plasmapheresis is continued for 2 days until normal platelet counts are reached and then discontinued without weaning. Daily folic acid is then prescribed.[4] Herein, we report a 6-year-old girl with diabetic ketoacidosis that was further complicated by TTP.

Case Report

The patient was a 6‑year‑old girl who was referred to the Emergency Room of Imam Hossein Hospital, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran.

How to cite this article: Mostofizadeh N, Arefnia S, Hashempour M, Dehkordi EH. Thrombotic Thrombocytopenic Purpura in a Child with Diabetic Ketoacidosis. Adv Biomed Res 2018;7:33.

Received: May, 2016. Accepted: July, 2016.
University of Medical Sciences with severe respiratory distress and in deep coma. The patient had a history of polyuria and polydipsia from 2 weeks before referral. No other significant medical history was noted. On clinical examination, the patient weighed 20 kg (50th percentile), and her height was 110 cm (50th percentile). Her Glasgow coma scale (GCS) was 5 (T = 36/5; blood pressure = 85/45; heart rate = 140, respiratory rate [RR] = 45) and the pupils were midsize and reacted toward light. Her blood glucose level was very high as measured by the glucometer device and venous blood gas (pH = 6.72, PCO$_2$ = 11, HCO$_3$ = 1). Therefore, the initial diagnosis of diabetic ketoacidosis was made based on laboratory findings [Table 1] and accordingly treated. Within 24 h after admission, her GCS score increased to 9 and blood gas indices were pH = 7/33, HCO$_3$ = 10, Be = −14, and PCO$_2$ = 19 mmg. About 48 h after admission and relative recovery from coma, the patient experienced generalized tonic–clonic seizure and was treated with phenobarbital and phonation to control the seizure and ventilated because of GCS = 5. Ventilator initiation setup was as follows: Synchronized intermittent mandatory ventilation, tidal volume: 180, RR: 16, positive-end expiratory pressure (PEEP): 4, and FIO$_2$: 60%. After 3 days, her consciousness improved and we changed ventilator setup to continuous positive airway pressure (support = 12. PEEP = 5. FIO$_2$ = 60%.

TTP was then suspected because of severe loss of consciousness, increased blood urea nitrogen-creatinine and oliguria, renal failure and anemia, thrombocytopenia, and high LDH. Computed tomography (CT) scan was done for the patient indicating no cerebral edema. Fibrinogen, D-dimer, peripheral blood smear, and ADAMTS13 tests were also requested. Schistocytes were observed in peripheral blood smear. Fibrinogen was normal, but D-dimer test was positive. ADAMTS13 could not be performed because we lacked the facility in Isfahan. We treated her with plasmapheresis for 5 days after that she became conscious. Plasmapheresis was done daily for the first 5 days until platelets reached 166 × 10$^9$ per liter and then tapered to twice a week for 1 week followed by once a week for 3 weeks. In each time, we pulled 1200 cc of plasma of plasmapheresis and substituted it for 500cc normal saline, 500cc FFP, and three vials of albumin 20%. Plasmapheresis had no complication in our patient. The patient was discharged in a good general condition and received insulin.

**Discussion**

TTP is the sudden onset of blood clots in blood vessels that could lead to thrombocytopenia and multi organ failure$^{[1]}$ occurring in various organs, especially the brain and kidneys with severe platelet thrombosis and reduced ADAMTS13.$^{[2]}$ In the typical form of the disease, the amount of ADAMTS13 decreases to <10% which differentiates TTP from hemolytic uremic syndrome. Ketoacidosis could lead to severe functional disorder in inflammatory cytokines such as IL-10, IL-1beta, TNF-alpha, IL-6, IL-8, and IL-2 which could in turn causes severe inflammation of the capillary.$^{[7]}$ Moreover, increased antigen factor 8 and von Willebrand factor indicate vascular endothelial damage in ketoacidosis.$^{[9]}$ The prevalence of TTP is 2–7 cases in 1 million annually and if left untreated, mortality rates increase to over 90%. High clinical suspicion and prompt treatment with daily plasmapheresis reduced mortality rates to 10–20%.$^{[1]}$ One study indicated that mortality rates decreased from 40% to 0% following plasmapheresis.$^{[9]}$ To the best of our knowledge, our case is the fourth case of TTP accompanied by diabetic ketoacidosis in children.

The first case was reported by Patra and Scott in 2011.$^{[2]}$ Khan et al. reported two other cases in 2013.$^{[1]}$ In all three girls who were 12, 13, and 14-year-old, diabetic ketoacidosis was initially diagnosed and the patients underwent fluid and insulin therapy, but then experienced renal failure, high LDH, thrombocytopenia, and high creatinine. Schistocytes were also seen in their peripheral blood smears indicating multiorgan failure. All three cases underwent daily plasmapheresis and had recovered. In the first reported case, because of abdominal pain further investigations were done and based on abdominal CT scan findings. The diagnosis of pancreatitis was made in the two other cases reported by Khan, no abdominal pain or other underlying disease except diabetes was noted as a risk factor for TTP. In both of these two cases, the clinical signs of thrombocytopenia, renal failure, loss of consciousness, evidence of microangiopathy in peripheral blood smear and

**Table 1: Laboratory results during hospital admission**

| Test          | Upon admission | Upon occurrence of TTP | On discharge |
|---------------|----------------|------------------------|--------------|
| BUN           | 35             | 60                     | 8            |
| Cr            | 0.9            | 2.7                    | 0.5          |
| CBC           | Hb=11.2, platelet=365,000 | Hb=8.9, platelet=62,000 | Hb=9.3, platelet=378,000 |
| AST           | 16             | 256                    | 25           |
| ALT           | 10             | 92                     | 23           |
| LDH           | 1455           | 730                    |              |
| PT            | 12.5           | 12                     |              |
| PTT           | 24             | 33                     |              |
| INR           | 1              | 1                      |              |
| VBG           | pH=6.72, PCO$_2$=11, HCO$_3$=1 | pH=7.02, PCO$_2$=15, HCO$_3$=4, Be=−27 | pH=7.45, PCO$_2$=40, HCO$_3$=24, Be=0.8 |

BUN: Blood urea nitrogen, Cr: Creatinine, CBC: Complete blood count, AST: Aspartate transaminase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio, VBG: Venous blood gases, TTP: Thrombotic thrombocytopenic purpura, Hb: Hemoglobin
increased LDH were seen. In our patient, schistocytes were also reported in the peripheral blood smear.

We started treatment based on clinical suspicion and laboratory evidences. Fortunately, the treatment was ultimately effective. In all reported cases, the patients referred with the loss of consciousness and diabetic ketoacidosis and later experienced renal failure, thrombocytopenia, and increased LDH (TTP), which was treated with plasmapheresis. Pancreatitis was not an underlying factor in our patient because she does not have abdominal pain, while it was noted in Patra and Scott study. [2] Similar to the mentioned study, we did not observe cerebral edema in our patient. All four mentioned cases in the literatures were girls and therefore further assessment should be done regarding the role of gender in TTP.

One of the limitations of our study was that we did not perform ADAMTS13 test because of the lack of related facility in Isfahan. In conclusion, TTP should be considered as a rare complication of diabetic ketoacidosis in patients with thrombocytopenia, renal failure, and reduced consciousness and should be immediately treated.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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