FATAL OUTCOME OF SPONTANEOUS CEREBRAL AND INTRAVENTRICULAR HEMORRHAGE IN A CHILD WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) – CASE REPORT

KRWAWIEŃIE DO OŚRODKOWEGO UKŁADU NERWOWEGO U DZIECKA Z SAMOISTNĄ MAŁOPTYLKOWOŚCIĄ (ITP) – OPIS PRZYPADKU

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Streszczenie

Wstęp: Małopłytkowość samoistna (ITP) jest najczęściej występującą, nabytą skazą krwotoczną u dzieci, charakteryzującą się przyspieszonym niszczeniem opłaszczonych przeciwciałami płytek krwi.

Pomimo dobrego rokowania ITP niesie ze sobą ryzyko ciężkich krwawień (głównie do ośrodkiowego układu nerwowego), które mogą zagrozić życiu dziecka.

Opis przypadku: Opisano przypadek 5-letniej dziewczynki z ITP oraz zakażeniem wirusem Ebsteina–Barra, u której doszło do tragicznego w skutkach krwawienia do ośrodkaowego układu nerwowego.

Wniosek: Autorzy chcieli zwrócić uwagę na bardzo rzadkie występowanie krwawień do ośrodkaowego układu nerwowego u dzieci z ITP i współistniejącym zakażeniem wirusem Ebsteina–Barra (prawdopodobnie będącym dodatkowym czynnikiem ryzyka krwawienia) oraz na zgon dziecka, pomimo zastosowania intensywnego leczenia.


Summary

Background: Idiopathic thrombocytopenic purpura (ITP) is the most prevalent acquired hemorrhagic diathesis in children characterised by antibody-mediated destruction of platelets. ITP is generally a self-limiting benign disorder but despite this good prognosis, ITP carries the risk of severe bleeding (mainly intracranial) that may threaten the child's life.

Case report: We describe a case of a 5-year-old girl with idiopathic thrombocytopenic purpura in the course of EBV infection with massive cerebral and intraventricular hemorrhage and fatal outcome.

Conclusion: This extremely rare case of intracranial haemorrhage in a child with ITP coexisting with EBV infection (a likely additional risk factor for hemorrhage) deserves attention considering the fatal outcome despite intensive treatment.

K e y   w o r d s: children – idiopathic thrombocytopenic purpura – EBV infection – intracranial hemorrhage.

Background

Idiopathic thrombocytopenic purpura (ITP), an autoimmune disorder characterized by antibody-mediated destruction of platelets, has an incidence rate of 4–8/100000 children/year making it the most prevalent acquired hemorrhagic diathesis in children [1, 2, 3, 4, 5]. ITP is generally a self-limiting benign disorder with a 60–80% chance of
spontaneous recovery occurring usually within a few months from onset [1, 5, 6].

In the 1950s, Harrington and coworkers disclosed the autoimmune etiology of ITP. The most common antigenic epitopes for antiplatelet antibodies in ITP are the platelet GPIb-IX and GPIIb/IIIa receptors. According to Psaila and Bussel [5], antibodies bound to platelet antigens opsonize platelets for clearance by FcγR-bearing cells, mainly in the spleen. The complement pathway may contribute to lysis of antibody-coated platelets in a small number of patients. The absence of detectable autoantibodies in some patients strongly suggests that additional mechanisms of platelet destruction are active. In this case, direct T-cell mediated cytotoxicity against megakaryocytes and platelets may be the main mechanism of thrombocytopenia [5].

Routine therapeutic modalities have little effect on specific mechanisms involved in the production and destruction of platelets, thus their usefulness in ITP is limited [1, 3, 5, 6]. Despite the generally good prognosis, ITP carries the risk of severe bleeding (mainly intracranial) that may threaten the child’s life [3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16]. The aim of this case report is to underline the extremely rare incidence of intracranial, life-threatening hemorrhage in a child with ITP probably caused by Epstein–Barr virus (EBV) infection and a fatal outcome of this complication despite aggressive treatment.

Case report

This 5-year-old girl was admitted to our Department with generalised cutaneous and mucous petechiae following symptoms of upper respiratory tract infection noticed one week earlier and treated symptomatically (powtórzenie, może inaczej opisać leczenie). Family history was unrevealing. Laboratory tests disclosed normal RBC and WBC counts, thrombocytopenia (< 10 G/L, normal range 150–400 G/L), normal coagulation screen, and normal LDH activity. Abdominal ultrasound demonstrated spleen enlargement to 9.8 cm (normal length for a 5-year-old girl is 4.9–5.8 cm). ANA, anti-dsDNA, ANuA, and anti-SM were negative. Immunoglobulin concentrations were within the normal range. ITP was diagnosed basing on the clinical course, laboratory findings, and bone marrow aspiration biopsy (increased number of megakaryocytes with immature structure). The quality of platelets was not evaluated nor antiplatelet antibodies were searched for. No signs of hypersplenism were noted. The extremely low platelet count (0–6 G/L) and upper and lower gastrointestinal tract bleeding episodes during 2 weeks before admission necessitated administration of steroids (2 mg/kg orally during seven days), intravenous immunoglobulins – IVIG (400 mg/kg/day during 5 consecutive days), and intravenous pulses of methylprednisolone (20 mg/kg/day) simultaneously with IVIG (1 g/kg/day) during three days. Clinical improvement was not achieved. Bleeding episodes were managed with platelet transfusions. The girl was discharged after 4 weeks in a good general condition and with a platelet count of 10 G/L, and was left on Rutinoscorbin (rutin + vitamin C) and Dicinon (Etamsilate). The parents were thoroughly informed as to ITP and its consequences. EBV infection (VCA IgM positive) was confirmed one week after discharge. The child was seen on a regular basis (every 2 weeks) at the Outpatient Department of Hematology. The platelet count increased spontaneously over the next two months, reaching 24 G/L. Three days later, during night-time, the girl developed speech disturbances, loss of consciousness, and epileptic seizures. She was immediately transferred to the intensive care unit (ICU). Hematology on admission was: HCT 42%, RBC 4.2 T/L, WBC 7.8 G/L, PLT 1 G/L. Cardiac arrest was managed with a successful resuscitation. Computer tomography scan confirmed massive intracranial hemorrhage (ICH) to the left frontal lobe and ventricular system with symptoms of increased intracranial pressure (fig. 1). High doses of platelet concentrates, i.v. pulses of methylprednisolone (20 mL/kg), and 2 g/kg IVIG were administered but without effect on the platelet count. Mannitol (1 g/kg/24 h in 6 equal doses) and furosemide (0.1 mg/kg/dose) 15 minutes after mannitol infusion were administered intravenously. The girl died on the 3rd day from admission.

Discussion

Intracranial hemorrhage belongs to the most severe, life-threatening complications of ITP in children and adults.
[1, 7]. Its frequency is relatively low and until 1998 only 74 cases of CNS bleeding associated with ITP were reported [3]. The risk of ICH in ITP is 0.1–1% and occurs predominantly in children with platelet counts below 10–20 G/L [3, 4, 8, 9, 10, 11, 12]. These data are consistent with our observations. More than 120 ITP patients were admitted to the Department of Pediatrics, Hematology and Pediatric Oncology (it is impossible to assess the exact number of children with ITP) between 1990 and 2008 and ICH occurred only in the present case. The patients usually experienced bleeding episodes after several weeks from the first symptoms of ITP [6, 11]. During the first days of ITP, episodes of ICH are extremely rare and the risk of bleeding is 0.1–0.2% [13, 14]. These data are consistent with our observations.

The onset of ITP in our patient was not associated with any clinically significant bleeding despite extremely low platelet counts (0–6 G/L). ICH occurred 12 weeks later when the platelet count was 1 G/L. It should be underlined that a spontaneous, gradual increase in platelet count was observed after discharge (the platelet count was 24 G/L three days before ICH).

Half of ITP patients have additional risk factors for ICH including malformation of cerebral arteries or veins, CNS injury, menstruation, infection (e.g. viral), autoimmune disease (lupus erythematosus), or medication [3, 4, 5, 6, 7, 12, 14, 15, 16]. Spontaneous ICH during ITP is seen in the remaining 50% of cases [7]. In our patient, brain injury, autoimmune disease, and medication were excluded. Neither angio-CT nor autopsy were done, thus we have no data regarding the presence of vascular malformations. However, EBV infection was disclosed. The mortality related to ICH in aggressively treated ITP patients does not exceed 50–55% [3, 4, 7, 11, 13]. However, Aryja et al. noted 6 deaths among eight children with ITP and ICH (75%) [6]. It should be noted that six of these children had chronic ITP at the time of presentation with ICH.

**Conclusion**

It seems that mortality is higher in ITP patients poorly responding to steroid therapy and/or intravenous infusion of immunoglobulins [6]. Our patient did not respond to high doses of platelet preparations, steroids, and IVIG during the ICH episode. The platelet count did not rise, even transiently. Moreover, neurosurgical intervention recommended by Medeiros and Buchanan, Lee and Kim, Woerner et al. in cases of progressive neurological deterioration or posterior fossa haemorrhage was not possible in our patient [10, 17, 18].

We draw attention to the total lack of response to treatment (before and during ICH), coexisting EBV infection (a likely additional risk factor for ICH), and a fatal outcome as a rare complication of idiopathic thrombocytopenic purpura in children.

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**References**

Commentary

The authors present a case of 5-year old girl with idio-pathic thrombocytopenic purpura (ITP) in the course of Epstein-Barr virus (EBV) infection complicated with intracerebral hemorrhage (ICH). ITP in childhood is usually an acute self-limiting disorder and despite very low platelet count is rarely complicated with serious bleeding. Therefore, the presented case merit attention due to several reasons. ICH as well as resistance to treatment with platelet infusion and intravenous steroids administration occur rarely in the course of ITP. The authors underline coexistence of these entities with EBV infection. They also stress the lack of possibility of neurosurgical intervention. However, in the report there is no mention regarding emergency splenectomy as a treatment for cases complicated with bleeding and lack of response to medical treatment. Aronis et al. estimate that response rate to splenectomy was 95%, and that it should be reserved for cases that fail to respond to conventional therapeutic modalities [1]. Several authors recommend neurosurgical intervention in cases of ICH in course of ITP stressing that it should be preceded by emergency splenectomy [2]. Humphreys et al. elaborated management plan for these rare and difficult patients [3]. It consists of immediate control of cerebral edema, emergency splenectomy, platelet transfusion and corticosteroids, cerebral angiography, and definitive neurosurgical procedure. Steroid treatment does not lower the incidence of ICH since significant number of patients develop ICH despite having already initiated steroid treatment of ITP [4]. What is more, only in 18% of cases with major hemorrhage traditional treatment lead to rise of platelet count [5]. Therefore, discussing the treatment of the analyzed case, it should be emphasized that emergency splenectomy is an important adjunct to the treatment modalities of complicated ITP patients.

In the presented case the entity of recurrent ITP took place with subsequent fatal complication. The aspect of ICH during recurrence of ITP is very interesting, and warrant further investigations to work out prophylactic therapy before incidence of the recurrence with all possible complications occur.

Active EBV infection seriously influenced resistance for treatment and fatal course in the presented case. It is known that neuroinfection caused by EBV can lead to ICH. It is characterized by spread of the hemorrhagic intracerebral changes that are very difficult to control. Morphology of intracerebral bleeding visible on the presented CT scan suggests that authors were probably dealing with such type of inflammatory changes.

Due to coincidence of rare complications, presentation of the case is an important contribution to the picture of ITP course and management. Comments made above are to supplement issues which I felt to be important in the discussion of the presented patient.

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References