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Letters to the Editor

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Dear Editor,

VITAMIN K DEFICIENCY BECAUSE OF CEFTRIAXONE USAGE AND PROLONGED DIARRHOEA

Vitamin K is synthesised by intestinal bacteria. This fat-soluble vitamin plays an important role in the synthesis of factors II, VII, IX and X in the liver. A minimal amount of vitamin K passes through the placenta, and a negligible amount is also found in breast milk. Factors including failure to administer vitamin K at birth, exclusive breastfeeding for a long period, prolonged or chronic diarrhoea, and prolonged use of antibiotics could lead to bleeding because of vitamin K deficiency.[1]

Ceftriaxone, because of its wide spectrum and easy administration, is a frequently used antibiotic. However, it decreases the activity of hepatic microsomal carboxylase and disrupts the metabolism of vitamin K, which can lead to a coagulation disorder and bleeding.[2] Coagulopathy and bleeding disorders are not common side effects of ceftriaxone. With this case, we wish to remind physicians of the possibility of this important side effect of ceftriaxone.

A 5-month-old male infant was referred to our clinic with mild dehydration. His medical history showed that he had attended another centre with a 10-day history of watery diarrhoea, having 10–15 motions per day. The presence of abundant leukocytes in the urine analysis led to a diagnosis of urinary tract infection, and ceftriaxone treatment was started. The pregnancy had been uneventful, and vitamin K was administered intramuscularly at birth. He was exclusively breastfed and had been supplemented with vitamin K. There was no bleeding history from his umbilical cord at birth.

His physical examination revealed body weight of 6420 g (10–25 percentiles) and length of 63.5 cm (10–25 percentiles). Dry mouth, sunken fontanel (1 × 1 cm in diameter), absent tearing, and diminished turgor and tone were the remarkable findings. Laboratory studies showed haemoglobin of 14.8 g/dL; total leukocyte count of 20 000/mm^3 with 30% neutrophils, and 70% lymphocytes and normal platelets; and platelet count of 598 000/mm^3. Biochemical parameters and blood gas analyses were all normal. Stool analysis and study for rotavirus were also normal.

After administering intravenous fluids for the moderate dehydration, ceftriaxone was concluded until the urine and stool culture results were concluded as negative.

On the third day of admission, bleeding in the form of oozing from orifices was seen, and subcutaneous ecchymosis developed in the same areas. Coagulation tests and other laboratory studies were repeated. Haemoglobin had decreased to 7.9 g/dL; total leukocyte count, platelets and biochemical parameters were normal. On the same day, the urine and stool culture results were negative. In the coagulation tests, fibrinogen was 90 mg/dL (normal (N) 180–350), D-dimer: 63 ug/L (50–300), prothrombin time (PT): 60 s (10–14), international normalised ratio (INR): 2.1 (0.8–1.2) and activated partial thromboplastin time (aPTT): 144 s (20–36). In spite of vitamin K supplementation at birth, high levels of PT and aPTT were suggestive of suspected vitamin K deficiency that may have developed secondary to a side effect of ceftriaxone. Ceftriaxone was ceased, and 3 mg intravenous vitamin K was administered. After the vitamin K administration, the bleeding and oozing from the orifices stopped within 2 h. At the sixth hour of treatment, PT was 25 s, INR was 1.4 and aPTT was 42 s, and a marked improvement in the clinical condition was noted. PT and aPTT levels measured at the 24th hour were within normal ranges.

On the sixth day of hospitalisation, the patient's diarrhoea had completely recovered with no other problems. He was then screened for cystic fibrosis, alpha-1 anti-trypsin and similar secondary diseases that could possibly have caused delayed haemorrhagic disease of the newborn. The sweat test and alpha-1 anti-trypsin levels were normal. A cranial ultrasonography was normal, and he was discharged from the hospital in good clinical condition.

Frequently used in the treatment of several infectious diseases (like meningitis, pyelonephritis and pneumonia), ceftriaxone is slowly eliminated, partly by the liver and partly by the kidneys. Except for its well-known side effects such as allergic reactions, gastrointestinal system disorders, nephrotoxicity and hepatotoxicity, it also reduces the activity of hepatic microsomal carboxylase via its N-methyl thiotriazone group. The exact mechanism of vitamin K-dependent haemorrhagic diseases caused by ceftriaxone has not been clearly described yet. However, it tried to be explained that all third-generation cephalosporins including ceftriaxone inhibits carboxylation of prothrombin. Deficient carboxylation of prothrombin results in reduced calcium binding and lower efficiency of prothrombin. Vitamin K is also required for this carboxylation process. A combination of deficient or less functional prothrombin production together with vitamin K deficiency is postulated for this coagulation disorder and bleeding.[3–5] In our patient, although vitamin K supplementation had been given at birth, long-standing diarrhoea and ceftriaxone usage probably led to the development of vitamin K deficiency.

In conclusion, vitamin K-dependent haemorrhagic diseases, though preventable with administration of 1 mg of vitamin K at birth, can still be observed at high rates in developing countries. The lack of vitamin K supplementation at birth, long-term nutrition with only breast milk, long-standing diarrhoea and antibiotic usage are among the causes of vitamin K-dependent haemorrhagic diseases. Vitamin K deficiency should be kept in mind in children using ceftriaxone and having long-standing

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diarrhoea. In the follow-up of these children, early diagnosis and prompt administration of vitamin K may be life saving.

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Dear Editor,

RENAL VEIN THROMBOSIS WITH PULMONARY EMBOLISM: FIRST MANIFESTATION OF LUPUS NEPHRITIS

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect almost any organ system, with renal involvement occurring in 90% of patients, while 50% of patients already have renal involvement at diagnosis.[1,2] Venous or arterial thrombosis can occur in SLE either as a result of anti-phospholipid syndrome or as a result of hypercoagulable state, related to nephrotic syndrome.[1,3–7] The risk factors for thromboembolic complications include hypoalbuminaemia, proteinuria, low plasma anti-thrombin-III (AT-III), increased fibrinogen level, hypofibrinolysis, decreased functional activity of protein C and its cofactor protein S, high haematocrit, thrombocytosis, increased platelet aggregation, hyperlipidaemia and reduced plasma volume.[1,3–7] An 11-year-old girl was admitted for a 2 months' history of fatigue and shortness of breath, and exercise-induced dyspnoea, headache and myalgia that occurred within the last 2 weeks. Three months prior to admission, there was a transient oedema of lower extremities. Her height was 141 cm (−1.2 standard deviation (SD)), weight was 29 kg (−1.4 SD) and body mass index was 14.6 (−1.2 SD); she presented with normal respiratory rate of 20/min, tachycardia (heart rate 111/min), elevated blood pressure (141/88 mm Hg), pallor, oedema of eyelids and lower extremities, and left flank pain with loin tenderness on palpation. Laboratory findings revealed anaemia: red blood cells 2.89×10^{12}/L (normal 4.10–5.10×10^{12}/L) and haemoglobin 7.6 g/dL (normal 11.5–15.5 g/dL). Among other abnormal results, the Coombs test was positive, D-dimers reached 17.66 mg/L (normal 0.00–0.50 mg/L, AT-III was 63% (normal 77–132%), and hypoalbuminaemia was 11.8 g/l, with low serum levels of total protein (53 g/L, normnal 65–80 g/L) and glomerular non-selective proteinuria (16 g/24 h). The following were normal: serum levels of cholesterol, blood urea nitrogen, creatinine (36 μmol/L), minerals (sodium, potassium, calcium, magnesium) and fibrinogen, white blood cell and platelet count. Urinary sediment contained 44 red blood cells/μL, 28 white blood cells/μL and 8 hyalin casts/μL. Ultrasonography revealed left renal vein thrombus (RVT) (25 mm in diameter) with preserved blood flow, pulmonary hypertension, and pericardial and pleural effusions (3–6 mm and 35–45 mm, respectively). Lung perfusion scan performed on the second day showed bilateral pulmonary embolism with multiple areas of hypoperfusion. Results of specific antibody profile were available on the third day, such as positive anti-nuclear antibodies (+++, analysed semi-quantitatively by immunofluorescence), positive antibodies to extractable nuclear antigen (ENA) ENA uridin-rich ribonucleoprotein (antigen expressed on protein components of small nuclear ribonucleoprotein particles) (U1 RNP), ENA RNP-Smith antibodies with negativity of ENA-SS-A/Ro antibodies to extractable nuclear antigen called Ro (or SS-A) (ENA -SS-A/Ro), antibodies to extractable nuclear antigen called La (or SS-B) (ENA-SS-B/La) and antibodies binding to double-strainded deoxyribonucleic acid detected by immunofluorescent technique (anti-ds-DNA IF). Anti-phospholipid antibodies were negative. Concerning hepatitis B and C status, hepatitis B surface antigen (HBsAg) and antibodies against hepatitis C (anti H-CV) antibodies were negative. There was mild hyperimmunoglobulinaemia (immunoglobulin (IgG) 22.9 g/L; normal 8.4–22.4 g/L) with elevated circulating immune complexes of 63 IU/L (normal <50 IU/L). C3 complement was in the normal range; C4 complement was low (0.13 g/L; normal 0.15–0.4 g/L). Renal biopsy was performed on day 4, resulting in the histological diagnosis of membranous nephropathy. Immunofluorescence on renal biopsy was positive in all IgG classes and C3 at the basal membrane with negative fibrinogen. Arthritis was diagnosed on magnetic resonance imaging of the joints. Therefore, the girl had severe nephrotic syndrome with left RVT and bilateral pulmonary embolism, and she fulfilled 6 criteria for the diagnosis of SLE (polyserositis, nephropathy, arthritis, haemolytic anaemia and leukopenia, positivity of anti-Smith antibodies and positivity of anti-nuclear antibodies) of 11.[2,3] Anti-thrombotic, immunosupressive and supportive therapy were started. She received low-molecular weight heparin (LMWH) 150 IU/kg/day for 3 weeks, three intravenous methylprednisolone pulses (30 mg/kg) followed by seven intravenous cyclophosphamide pulses (750–1000 mg/m^2) every 3–4 weeks, and further maintenance therapy with azathioprine (2 mg/kg/day) and oral methylprednisolone (1.5 mg/kg) in tapering dose. Treatment included albumin infusion, diuretics, enalapril, losartan, felodipin, intravenous IgGs and cotrimoxazol prophylaxis. Anti-thrombotic therapy resulted in complete re-canalisation of left renal vein. The patient was further maintained on daily subcutaneous enoxaparin for 12 months. Complete remission of lupus nephritis was achieved after 5 months from onset of therapy. Thromboembolism in our patient was not

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