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CASE REPORT

Chronic coagulopathy in a patient with argininosuccinase deficiency

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Argininosuccinase deficiency (McKusick 20790) (ALD) is an autosomal recessively inherited inborn error of the urea cycle. The neonatal form presents with hyperammonaemia and encephalopathy. The survivors have intellectual impairment and varying degrees of hepatomegaly associated with mild abnormalities of liver functions (Batshaw *et al.*, 1982). Although the hepatomegaly is present in the first few weeks of life and the synthetic function of the liver is preserved, the long-term outcome for the liver is unknown (Flick *et al.*, 1986). We report vitamin K non-responsive coagulopathy secondary to chronic liver disease in a patient with argininosuccinase deficiency.

R. W., an 8-year-old girl, presented with hyperammonaemic coma and seizures on the third day of life. Diagnosis of ALD was based on markedly elevated plasma levels of argininosuccinic acid and mildly elevated citrulline. It was confirmed by fibroblast assay of argininosuccinase which showed only 4.8% of normal activity. She was rescued from the coma with exchange blood transfusion, mechanical ventilation and other supportive therapy. Her subsequent treatment has consisted of a low protein diet (1.25–2 g/kg/day) and supplementary arginine as the free base (0.5–0.75 g/kg/day). She has had numerous episodes of hyperammonaemia manifesting with seizures and lethargy, especially during intercurrent infections. She has been given sodium benzoate 250 mg/kg/day during hyperammonaemic periods along with intravenous arginine. She remains stable but has mild spastic cerebral palsy, walks with a wide-based gait and has an IQ of 30. Her height is at the 3rd centile and weight and head circumference are at the 10th centile. Her peripheral blood count, total serum protein and albumin levels are normal. Her plasma ammonia ranges from 50–60 μmol/L (normal 24–48) and her plasma argininosuccinic acid level ranges from 520–846 μmol/L. The alanine aminotransferase and aspartate aminotransferase levels fluctuate from 45–250 MU/ml, but serum bilirubin and alkaline phosphatase are normal.

During the past two years prolonged bleeding at venipuncture sites prompted us to study her coagulation status. Prothrombin time (PT) was 16.7 s (control 12.3), partial thromboplastin time (PTT) was 50.7 s (control 24–38) and thrombin time was 12.9 s (control 10.7–14.8). The fibrinogen level was 1.35 g/L (normal 1.64–3.66). Prolongation of PT and PTT was persistent on several occasions. Her platelet count ranged from 200×10^9 to 290×10^9/L and the platelets appeared well clumped on the peripheral blood smear. No antibodies against hepatitis A, B, cytomegalovirus,

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Epstein–Barr virus or human immune deficiency virus were detected. Activities of coagulation factors II (55% of normal), V (37% of normal), IX (47% of normal) and protein C antigens (63% of normal) were decreased, whereas activities of VII (95%) and X were normal. Fibrin split products were (1:5) negative. Inhibitor screen to detect a circulating anticoagulant was negative. Antithrombin (AT III) was normal (95%).

PT and PTT did not show any improvement after intravenous administration of vitamin K or after transfusion with fresh frozen plasma (FFP). In fact, the PTT was further prolonged 2 and 24 h post-FFP transfusion and the plasma ammonia rose from 53 to 88 μmol/L in 2 h.

To our knowledge, this is the first report of chronic coagulopathy in a patient with argininosuccinase deficiency. 18 children with ALD followed up to the age of 5 years were reported to have hepatomegaly and ultrastructural changes in hepatocytes but normal synthetic liver functions (Flick *et al.*, 1986). Our patient has shown decreased synthesis of various coagulation factors in the liver independent of hyperammonaemia. We speculate that the argininosuccinase deficiency causes progressive liver disease and may eventually lead to liver failure. The increase in ammonia and PTT after fresh frozen plasma transfusion suggests that the protein load of FFP aggravated the liver dysfunction.

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