Mixed Coagulopathy in Patient with Peroxisomal Disorder, Zellweger Syndrome

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Title: Mixed Coagulopathy in Patient with Peroxisomal Disorder, Zellweger Syndrome

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Protime	PT
Activated Partial Thromboplatin Time	aPTT
Alanine Transaminase	ALT
Aspartate Transaminase	AST
Dihydroxycholestanoic Acid	DHCA
Trihydroxycholestanoic Acid	THCA

Dear Editor:

Peroxisome biogenesis disorders including Zellweger Syndrome can present with severe bleeding due to hepatopathy and coagulopathy.[1] Pathogenesis can include both synthetic and secondary ADEK vitamin deficiencies. While almost 50% of patients with Zellweger will have minor bleeding, 13% of patients were reported

to have intracranial bleeding.[1]

We care for an infant girl, born full term with initial newborn screen findings of elevated very long-chain fatty acids. Genetic testing demonstrated compound heterozygous mutations of the PEX12 gene: pathogenic c987_988del (p.Phe330Serfs*23) and variant of uncertain significance c368_370del (p.Leu123del). Initial newborn care included vitamin K injection and standard care until the age of 5 months old. Due to altered mental status and vomiting, she presented to the emergency department; there was no reported inciting event. Head imaging demonstrated subdural hematomas with mass effect and midline shift. Hemostatic testing found prothrombin time (PT) >100s, normal activated partial thromboplastin time and factor 7 activity of 2%. She also had anemia to 3.5g/dL, reticulocytosis, leukemoid reaction and normal platelet count. Liver function found aspartate aminotransferase (AST) 111, alanine aminotransferase (ALT) 46, normal fibrinogen by Clauss. PT mixing study normalized initially and stayed corrected.

She was treated with activated factor 7, as well as appropriate transfusion and supportive measures. She was started on IV vitamin K and transitioned to oral vitamin K and exogenous cholic acids. Due to persistently low levels including with parenteral administration, factor 7 gene was analyzed and found to have no pathogenic mutations. Over the next 7 months, she remained on oral vitamin K (both as tablet and liquid formulation); factor 7 remained persistently between 24 and 45%. Des-gamma-carboxy prothrombin levels were found to be 1.1 (normal 0-7.4 ng/mL). Most recent factor 7 activity level of 45% was achieved with liquid vitamin K 5mg daily. Bile acid intermediates dihydroxycholestanoic acid (DHCA) and trihydroxycholestanoic acid (THCA) were initially markedly elevated; DHCA has trended down.

While on oral vitamin K, Protein C was found to be low at 43% while having normal factors 5, 8, 9 and protein S. She had a persistent anemia with reticulocytosis and low vitamin E level (1.8 alpha-tocopherol, normal 3.5-8.0 mg/L). After starting ADEK vitamins her anemia resolved due to presumed vitamin E deficient hemolytic anemia. Other than with a recent illness, transaminase elevation and cholestasis improved; synthetic function remained stable. She has been growing on elemental formula. Her only bleeding since initial presentation was a brief episode of self resolved hematochezia.

Our patient is an example of an otherwise spontaneous hemorrhage due to secondary coagulopathy with a genetic predisposition and associated malabsorption. Our patient benefited from a multidisciplinary approach including hematology, gastroenterology, genetics and neurosurgery. Considerations for future research in patients with peroxisome disorders could include prophylactic ADEK vitamins though response to IV and oral supplementation has been mixed.

Conflicts of Interest: The authors have no conflicts of interest.

Zeynelabidin S, Klouwer FCC, Meijers JCM, Suijker MH, Engelen M, Poll-The BT, van Ommen CH. Coagulopathy in Zellweger spectrum disorders: a role for vitamin K. J Inherit Metab Dis. 2018 Mar;41(2):249-255. doi: 10.1007/s10545-017-0113-8. Epub 2017 Nov 14. PMID: 29139025; PMCID: PMC5830475.