

Supplemental Material

Title: Pseudohyponatremia: Mechanism, Diagnosis, Clinical Associations and Management

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Section S1-Clinical conditions causing increased serum solid content

Conditions causing hyperproteinemia

Hypergammaglobulinemia represents a major laboratory feature of various forms of hepatitis or cirrhosis [153]. High SSC in such patients may be caused by both hyperproteinemia and hypercholesterolemia from biliary obstruction as noted earlier. Interferon administration represents another source of hyperproteinemia [153–154]. Hyperproteinemia is caused by elevated levels of light chains, almost always of the lambda type, in POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome [168] and by high blood levels of inflammatory cytokines in Castleman's disease [169]. Hypergammaglobulinemia is encountered in 25%-91% of the cases and monoclonal gammopathy in 1%-35% of the cases of Gaucher's disease, which is an autosomal recessive lysosomal storage disease caused by mutations of the 1q21 GBA1 gene located in chromosome 1 [170].

Conditions causing hypertriglyceridemia

Excessive ethanol consumption leads to hypertriglyceridemia through increased secretion of VLDL, impaired lipolysis and increased fluxes to the liver of fatty acids from adipose tissue. Obesity increases the risk of severe hypertriglyceridemia secondary to ethanol consumption [171]. Alpha-interferon and other cytokines stimulate lipid synthesis in the liver [172]. Administration of alpha-interferon for treatment of hepatitis C led repeatedly to transient, but pronounced, increases in serum triglycerides [173]. Several studies document hyperlipidemias in diabetic patients [174-183]. Type 2 and poorly controlled type 1 diabetes mellitus and obesity lead to increased peripheral lipolysis, increased delivery of fatty acids to the liver and hypertriglyceridemia [174]. Juvenile diabetics may have combined hypercholesterolemia and hypertriglyceridemia [181]. Type 2 diabetics have frequent hyperlipidemias, including types II, IV, and combined types II and IV [183]. Hypertriglyceridemia constitutes the dose-limiting toxicity of the antineoplastic agent all-trans-retinoic acid (ATRA) [184].

Conditions causing hypercholesterolemia and/or combined hyperlipidemia

Cholestasis with elevated serum levels of lipoprotein X has caused pronounced hypercholesterolemia in graft-versus-host disease with liver involvement [185] and non-Hodgkin's lymphoma [186]. Nephrotic syndrome secondary to various types of glomerular disease causes changes in multiple proteins involved in the metabolism of lipids [187] resulting

in severe combined hyperlipidemia and hypercholesterolemia [187–190]. In this case, spuriously low [Na]_s measurements will be reported by indirect ISE only in cases in which the increase in SSC caused by hyperlipidemia is larger than the decrease secondary to low serum protein values.

In hemophagocytic lymphohistiocytosis, a syndrome characterized by abnormal activation of T-cells and overproduction of inflammatory cytokines, hypertriglyceridemia and hypercholesterolemia are frequent laboratory findings [191–192]. Various preparations of infused lipid emulsions result directly in hyperlipidemia, but also increase the risk of hepatic damage [193–194] including cholestasis [195]. The risk of hypertriglyceridemia in COVID-19 patients receiving parenteral nutrition was increased by simultaneous administration of lopinavir/ritonavir or propofol and the presence of obesity [196]. Koch and coauthors evaluated in vitro pseudohyponatremia in serum samples containing lipid preparations and advocated the use of direct ISE for measuring [Na]_s at lipemia indices above a cut-off value of 700 [197].

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Preventing pseudohyponatremia: Intralipid^R-based lipemia cutoffs for sodium are inappropriate.
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