Exposure to inorganic arsenic (iAs) in drinking water is a global public health concern and is associated with a range of health outcomes, including immune dysfunction. Children are a particularly sensitive population to the effects of inorganic arsenic, yet the biological mechanisms underlying adverse health outcomes are understudied. Here we used a proteomic approach to examine the effects of iAs exposure on circulating serum protein levels in a cross-sectional children's cohort in Mexico. To identify iAs-associated proteins, levels of total urinary arsenic (U-tAs) and its metabolites were determined and serum proteins assessed for differences in expression. The results indicate an enrichment of Tumor Necrosis Factor-(TNF)-regulated immune and inflammatory response proteins that displayed decreased expression levels in relation to increasing U-tAs. Notably, when analyzed in the context of the proportions of urinary arsenic metabolites in children, the most robust response was observed in relation to the monomethylated arsenicals. These data represent the first assessment of protein expression in serum in adolescents exposed to inorganic arsenic. The proteomic differences in expression seen here highlight the role of iAs in possibly impacting maturation of the immune system during a critical period of development and, as such, has the potential to alter disease risk later in life.