Nephrogenic Syndrome of Inappropriate Antidiuresis: Congenital and Acquired

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The ‘syndrome of inappropriate secretion of antidiuretic hormone (SIADH)’ is characterized by unregulated or elevated inappropriate secretion of arginine vasopressin (AVP). Among patients with clinical features SIADH, however, a small subset of patients may have undetectable levels of AVP. To include this type of patients, nephrogenic syndrome of inappropriate antidiuresis (NSIAD), the term ‘syndrome of inappropriate antidiuresis (SIAD)’ was proposed instead of SIADH. Thus, SIAD can be divided into SIADH and NSIAD according to whether AVP release in increased or suppressed.
Initially NSIAD was reported from two infants, who were identified to have gain-of-function mutations in the vasopressin type 2 receptor (V2R) gene (R137C and R137L). Interestingly, NSIAD with the R137C mutation was also identified in adult hyponatremic patients who resisted V2R antagonist treatment. As expected, hyponatremia may be uncertain in female heterozygotes. Later, two more gain-of-function mutations in V2R gene were identified: F229V and I130N. In contrast with the R137C mutant, the activity of F229V and I130N mutant was reversed by V2R antagonist treatment.
In addition to these congenital cases of NSIAD, we need to pay attention to acquired causes of NSIAD. Among drugs causing SIADH, the stimulation of AVP release was demonstrated in only a few. Instead, it was postulated that some drugs may potentiate action of AVP in the kidney. Recently, drugs including sildenafil, statins, and cyclophosphamide were shown to activate aquaporin-2 (AQP2) in the kidney in vitro or ex vivo. They can induce hyponatremia in vivo in the absence of AVP, suggesting acquired causes of NSIAD.
It may be necessary to explore the possibility of NSIAD in patients who were previously diagnosed as idiopathic SIAD.