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A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis

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The syndrome of inappropriate antidiuretic hormone secretion (SIADH), also referred to as syndrome of inappropriate antidiuresis (SIAD), is the most common cause of hyponatremia characterized by extracellular hypotonicity and impaired urine dilution in the absence of any recognizable nonosmotic stimuli for the antidiuretic hormone arginine vasopressin (AVP). Hyponatremia in SIADH is primarily the result of excessive water retention caused by a combination of inappropriate antidiuresis and persistent fluid intake in the presence of impaired osmoregulated inhibition of thirst. It is sometimes aggravated by a sodium deficiency caused by a decreased intake or a secondary natriuresis in response to elevated extracellular volume. Inappropriate antidiuresis usually results from endogenous production of AVP that can be either ectopic (from a malignancy) or eutopic (from the hypothalamus/neurohypophysis). Regardless of its origin, different types of osmotic dysregulation of AVP have been reported with possibly fundamental deviations in treatment need and efficacy. A recent quantitative analysis of 50 patients with SIADH, which underwent

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serial measurements of copeptin during hypertonic saline infusion, revealed five distinct types of osmoregulatory defect ("type A to E") without affiliation to specific underlying diseases. In addition to apparently impaired osmoregulated inhibition of AVP release in the majority of patients, 12% of patients showed an AVP-independent mechanism of inappropriate antidiuresis, whilst 20% of them presented a reverse relation between hormone release and serum osmolality, presumably related to interrupted nonosmotic inhibitory pathways. The interference of these different types of SIAD with clinical presentation and therapy response will be a relevant subject for future research.

Introduction

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of euvolemic hyponatremia and the single most prevalent cause of hypoosmolality. Its prevalence ranges from 40% to 70% among all hypoosmolar patients [1,2]. It mainly develops from insufficient suppression of the antidiuretic hormone arginine vasopressin (AVP) at times when physiologic AVP release from the posterior pituitary would normally be suppressed. Consequently, a decrease in osmotic pressure of body fluids associated with impaired urinary dilution is the hallmark of SIADH and led to its first description by William B. Schwartz and Frederic Bartter in 1957 [3]. Only with the development of first specific radioimmunoassays in the 1970s, enabling to sensitively quantify AVP in the circulation [4], much has been learned since then about the specific character of SIADH, the variety of clinical settings associated with inappropriate AVP secretion beyond ectopic synthesis (Table 1) as well as its diagnostic differentiation from other causes of hyponatremia [5–8]. Importantly, with the recent approval of competitive vasopressin receptor antagonists in the United States and in Europe, a new class of drugs has become available which offers the opportunity for a specific treatment of SIADH by selectively increasing the urine aquaresis [9,10]. Still, it is surprising how rudimentary our understanding of this syndrome remains more than half a century after its first description in terms of basic aspects of pathophysiology.

It appears appropriate, therefore, to begin this article with a brief summary of some more general aspects of disturbed AVP function in SIADH before discussing more recent findings about various osmoregulatory defects of SIADH as well as their possible impact on clinical manifestation and treatment response.

Pathophysiology of SIADH

The syndrome of inappropriate antidiuretic hormone secretion is a disorder of fluid and sodium homeostasis, characterized by hypotonic hyponatremia and impaired urinary dilution in the absence of any identifiable secondary ("appropriate") causes of nonosmotic AVP release [11]. Consequently, SIADH is a diagnosis of exclusion and must be differed from other forms of hypo-, hyper- and euvolemic hyponatremia with fundamentally different abnormalities in sodium and fluid balance and distinct treatment requirements. Although the fundamental cause of hyponatremia in SIADH is an absolute increase in total body fluid resulting from elevated fluid intake on the basis of impaired compensatory urine dilution, it must be noted that the net increase in water content fails to account entirely for the decrease in serum sodium levels [12]. In fact, secondary natriuresis and kaliuresis that occur during the establishment of SIADH further contribute to the decrease in body solutes and promote, at least in part, the hypoosmolality [13]. This solute loss mainly serves to counteract the increase in extracellular volume at the expense, however, of making the hyponatremia worse. Studies of whole body fluid and electrolyte content demonstrate that the relative contributions of water retention and solute losses