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Inappropriate Arginine Vasopressin Levels and Hyponatremia Associated with Cyclic Vomiting Syndrome

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Key Words

Vomiting · Hyponatremia · Vasopressin

Abstract

We herein describe two children who presented with attacks of severe cyclic vomiting. The primary case was a 2.5-year-old girl with a history of several admissions with vomiting and altered mental status. She was diagnosed with cyclic vomiting syndrome (CVS). During her attacks she developed significant hyponatremia on several occasions, which prompted us to measure plasma arginine vasopressin (AVP) levels during attacks. We found inappropriately high AVP levels with concomitant hyponatremia. We also measured plasma AVP and plasma sodium in another child with CVS who did not develop manifest hyponatremia but showed inappropriately elevated plasma AVP levels. Since the standard treatment of CVS consists of fluids, high plasma AVP levels may lead to dilutional hyponatremia. We would therefore like to emphasize the importance of close assessment of electrolyte levels in patients with CVS to avoid water intoxication.

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Introduction

Cyclic vomiting syndrome (CVS) was first encountered in the literature in 1861 and the main clinical features were described 21 years later. CVS is an uncommon condition in childhood with an elusive pathophysiological background and a good long-term prognosis. The diagnosis is often challenging, frequently resulting in repeated visits to emergency departments. The diagnostic criteria are three or more recurrent discrete episodes of vomiting, with symptom-free intervals between episodes, and absence of clinical, laboratory and radiographic evidence suggestive of another disease or condition. Episodes are stereotypical in terms of timing of onset, symptoms and duration [1]. Children experience on average

12 cycles of vomiting per year [2]. Trigger factors are not uncommon and can comprise stress, infections and lack of sleep. The typical age at onset is early childhood and the syndrome can give place to typical migraine in adolescence and to a lesser degree persist into adulthood.

The pathogenesis of the disease is still unknown, although it is hypothesized that there is a connection between migraine and CVS [3], with high response rates to anti-migraine therapy further supporting this notion. CVS has also been linked to metabolic and mitochondrial disorders, and mitochondrial DNA deletions in children have been described to contribute to the pathogenesis [4]. A family with four members suffering from CVS has also been identified [5], indicating a genetic component of the disorder. Due to the mitochondrial hypothesis, multiple mitochondrial-targeted therapies have been developed, and it is suggested that co-enzyme Q10 and L-carnitine may have an effect [6].

The hormones of the hypothalamic-pituitary-adrenal axis have been related to CVS. Sato et al. [7] described two children with markedly increased pituitary hormones in plasma, including arginine vasopressin (AVP) and adrenocorticotrophic hormone, during attacks of cyclic vomiting. Decreased intravascular volume and nausea [8] are potent stimuli for AVP secretion, but Kim et al. [9] also showed that AVP per se may induce nausea when administered intravenously (0.1 U/min).

The initial treatment for children with an episode of CVS is intravenous fluid therapy, preferably with dextrose solutions [10], anti-emetic therapy, and if necessary analgesics. If the attacks are very frequent and severe, prophylactic treatment with migraine agents such as amitriptyline or cyproheptadine can be considered [11]. Recently valproate, a drug with a known effect on epilepsy, has also been shown to be effective as a prophylaxis for CVS [11]. The mechanisms by which valproate exerts its effects are not yet fully understood, but it seems to increase levels of gamma-aminobutyric acid in the brain and to inhibit sodium channels. We herein describe two cases of CVS: one with inappropriately high plasma AVP levels and concurrent dilutional hyponatremia, and one with inappropriately high plasma AVP levels and no signs of dilutional hyponatremia.

Case Presentation

The primary case (case 1) concerns a 2.5-year-old girl who was admitted with severe vomiting and dehydration. She was of Philippine and Danish origin and had previously been diagnosed with Turner's syndrome. Since the age of 13 months she experienced recurrent attacks of severe vomiting. The onset of the vomiting episodes was rapid, could consist of up to 50 vomits per day and the duration of an episode was usually 1 week. Based on the clinical characteristics and the absence of other signs of disease, the girl was diagnosed with CVS.

During one of these episodes the girl was admitted with ongoing vomiting and fever, but no clinical signs of dehydration. The initial plasma sodium (PNa) was 133 mmol/l, plasma potassium was 3.4 mmol/l and hematocrit was 33%. At this point plasma AVP was inappropriately high at 3.17 pg/ml, with a concurrent plasma osmolality at 276 mosm/kg (fig. 1, the specific measurement is marked by an asterisk). She was treated with intravenous glucose 10% with 20 mmol Na/l and 20 mmol K/l at a rate of 40–50 ml/h. The day following admission PNa further declined to 131 mmol/l. During the following days the vomiting slowly improved and PNa returned to normal levels. The girl was discharged after 10 days.

Subsequently, the girl developed hyponatremia on several occasions during her attacks, with PNa values as low as 129 mmol/l. Over a 1-year period she was followed with plasma AVP measurements on 7 occasions (fig. 1). Several of these values were inappropriately high

compared to the concurrent PNa levels. Following the tenth attack the girl was treated with valproate (25 mg/kg/day), and the attacks ceased. After more than 2 years of follow-up she is still free of symptoms.

The other case (case 2) concerns a boy, with Somalian parents, born and raised in Denmark. At the age of 7 he was admitted to the hospital with fever, vomiting and diffuse pain in his abdomen. This incidence was considered to be gastroenteritis. At the age of 9 he starts to vomit periodically, with high frequency and rapid onset of vomits. During a period of 1 year he had 9 episodes, with 1–2 months between attacks. Normally, he improved after 2 weeks of intravenous fluid therapy. During an admission, he presented with PNa of 147 mmol/l, plasma AVP of 5 pg/ml, plasma osmolality of 292 mosm/kg and no clinical signs of dehydration. Three days later, after fluid therapy with glucose solutions, his PNa had decreased to 136 mmol/l, but he did not develop significant hyponatremia during his admission. We measured plasma AVP levels on three other occasions (fig. 1). After the ninth attack he was commenced on valproate (15 mg/kg once daily) as prophylaxis, with prompt effect. He ceased taking the medicine after 8 months and did not experience any symptoms after this.

Discussion

The initial treatment for CVS is fluid replacement, not only to cover the fluid losses that can be seen during attacks, but it also seems that dextrose solutions may have a direct effect on the condition [12]. However, patients should be closely monitored while on intravenous fluids and electrolytes measured in order to avoid episodes of dilutional hyponatremia, which can result in significant neurological symptoms. Body weight, urine production rate and if possible urine osmolality can be used as indicators of hydration status. Anti-emetics may be given to ease the patient's nausea. Between attacks the treatment must be focused on preventing new attacks. CVS is a disease of unclear pathophysiology and is defined by the characteristics of the vomiting episodes. We herein describe a girl with CVS who experienced episodes of significant hyponatremia during admission and fluid therapy, and a boy who presented with inappropriately high plasma AVP levels during his attacks. Markedly increased levels in plasma AVP have previously been demonstrated in adults with induced nausea [13]. Since we only have a limited number of plasma AVP measurements, it is difficult to directly compare the plasma AVP levels of our patients with the levels seen in that study. Furthermore, it must be noted that in the other study nausea was medically induced, a less physiological clinical setting. Due to the limited number of plasma AVP measurement assessed in our patients during admissions and since AVP has a very short half-life, it is not possible to evaluate whether the values were even higher. The inappropriately high plasma AVP values seen during CVS attacks suggest a role of AVP in the development of hyponatremia. These observations draw attention to this potential serious complication of fluid therapy in children with CVS.

In case 1, hyponatremia ensued during intravenous fluid administration, which represents the first-line treatment of CVS episodes. AVP is secreted from the neurohypophysis in response to osmotic stimuli or hypovolemia. However, a potent stimulus for AVP secretion is nausea, which can lead to excess AVP secretion, and this seems to be the case in children with CVS, as intense nausea is one of the landmark symptoms. This series of events puts the patient at risk for hyponatremia should the intravenous fluid therapy not be adjusted appropriately.

The increased plasma AVP levels seen in the present cases may not just be the result of the intense nausea per se, but may also be part of CVS pathophysiology, as several studies,

both in humans and animals, suggest a role for AVP in mediating nausea [13, 14]. It is however more plausible that the initial episode of vomiting stimulates AVP secretion, thus leading to anti-diuresis and water retention, and the resulting hyponatremia further stimulates nausea and vomiting. Hyponatremia influences the mental status of patients [15], leading to confusion, irritability and fatigue. In figure 1, plasma AVP measurements of both cases during clinical control visits are also shown, and these were within the normal range, thus supporting the thesis.

The first-line treatment of CVS is intravenous fluid replacement with 10% dextrose solutions [12]. In case of inappropriately high plasma AVP levels, this may lead to a significant fall in PNa. Care should therefore be taken when prescribing fluids in children with CVS, with close monitoring of clinical and laboratory values. A similar line of events is seen in the syndrome of inappropriate anti-diuretic hormone secretion where the patients are effectively treated with fluid restriction.

Conclusion

The diagnosis of CVS is clinical, with stereotypical episodes of vomiting, altered mental status and lack of other signs of disease. Inappropriately high plasma levels of AVP seem common during the attacks in children with CVS, potentially aggravating the symptoms. Close clinical monitoring (body weight, hydration status, urine output, serum electrolytes) of patient with CVS while on intravenous fluids is essential in order to avoid episodes of dilutional hyponatremia. It is important to adequately evaluate PNa levels to avoid fluid overloading of children with CVS.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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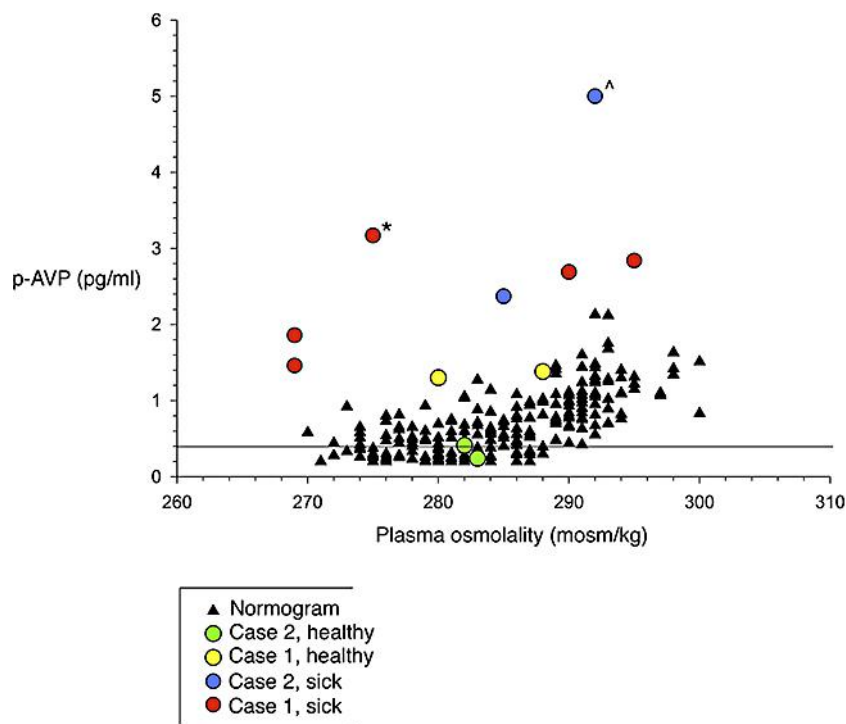


Fig. 1. The cases were followed with plasma AVP (p-AVP) measurements 7 and 4 times, respectively, both during clinical controls where they were clinically well and during admissions with attacks of CVS. The values marked by an asterisk and a caret were taken during the attacks described in the text.