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Diagnosis and Management of Neonatal Central Diabetes Insipidus: Expert Opinion

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Abstract **Original Research Article**

Diabetes Insipidus is a heterogeneous clinical syndrome of disturbance in water balance, characterized by polyuria, polydipsia and failure to thrive. The clinical presentation varies with age of onset and underlying etiology. There is no clear consensus among pediatric endocrinologists on managing neonates with diabetes insipidus. Diagnosis is based on the presence of high plasma osmolality and low urinary osmolality with significant water diuresis. Water deprivation test is useful in establishing a diagnosis of diabetes insipidus and helps differentiating between nephrogenic diabetes insipidus and central diabetes insipidus. However, is difficult to be performed during neonatal age. Fluid management is the most safe approach to treat. Desmopressin, although is the drug of choice for CDI therapy, however during neonatal period, fluid management with or without thiazide is preferred. In this survey, we analyzed the responses of 35 pediatric endocrinologists regarding neonatal diabetes insipidus management, and their recommendations were reported.

Keywords: Diabetes Insipidus, water balance, underlying etiology, polydipsia, Desmopressin.

INTRODUCTION

Diabetes Insipidus (DI) is characterized by the inability to concentrate urine secondary to vasopressin deficiency or to vasopressin resistance resulting in polyuria. DI is rare, with a prevalence estimated at 1:25,000; fewer than 10% of cases are hereditary in nature [1]. Central DI (CDI) accounts for greater than 90% of cases of DI and can present at any age, depending on the cause. No prevalence for hereditary causes of CDI has been established [1].

Neonatal central diabetes insipidus (NCDI) can be a result of intracranial insult, either congenital or acquired [1]. The management NCDI poses special set of problems owing to obligate high water intake in milk-based feeds [2]. Due to the risk of hyponatremia on long term anti diuretic hormone, these babies should be managed on high volume of feeds with low content of renal solute load [3]. Addition of thiazides may decrease the fluid requirements in these patients [4-8]. In this report, we reviewed the NCDI management recommendations and expert opinion of 35 pediatric endocrinologists from Saudi Arabia.

METHODS

A questionnaire was distributed regarding the diagnosis and management of NCDI to 135 pediatric endocrinologists. Thirty-five endocrinologists completed the survey. The questionnaire included years of experience the endocrinologist has spent in this field. The number of cases he or she is currently following. The most common congenital etiology of NCDI in his/her series and the age of diagnosis. The initial management plan and whether it includes thiazide or desmopressin therapy as a part of fluid management. The dose and route of desmopressin administration and the target sodium level. The answers were analyzed by the authors of this manuscript.

RESULTS

Thirty-five board certified pediatric endocrinologists completed the survey with a mean of 5-year experience in the specialty of pediatric

endocrinology (range from 3-11 years). The total number of cases seen was 19 cases in the last year. The etiology was idiopathic in the majority of cases. Five cases were premature with intra cranial hemorrhage, 4 cases with a history of asphyxia, 4 cases had holoprosencepahly, 2 cases were suspected to have septo-optic dysplasia. No genetic tests were performed for these cases. All endocrinologists agreed that the initial diagnosis depends on increased urine output more than 5 cc/kg/hour, hypernatremia and elevated plasma osmolality, together with an inappropriately low urine osmolality. None of the participating endocrinologists recommended water deprivation test at this neonatal age.

At the time of hypernatremia, the mean serum and urine osmolality values were 310 ± 9 mOsm/kg and 179 ± 48 mOsm/kg, respectively. The mean serum sodium level was 156 ± 4mmol/l. Antidiuretic hormone levels were not checked in our patients. After initiating thiazide and/or desmopressin, serum sodium levels returned to normal within 2-3 days.

All endocrinologists agreed that the goal of treatment is to decrease urine output while allowing for appropriate fluid balance, and ensuring normonatremia. An infant's obligate need to consume calories as liquid and the need for readjustment of medication dosing in growing neonates both present unique challenges for diabetes insipidus management in the pediatric population.

All endocrinologists believed that treatment modalities typically include vasopressin or thiazide diuretics. Thirty endocrinologists used only thiazide in their management of NCDI and 5 endocrinologists used both. Hydrochlorothiazide was used at a starting dose of 1-2 mg/kg/day. Thiazides was stopped in 5 children due to lack of response. No history of hyponatremia nor hypercalcemia. Desmopressin acetate is available in Saudi Arabia in different forms. As subcutaneous/intravenous injectable form 4mcg/ml in multiple-dose vial, the starting dose is ranging from 0.5-1mcg, as aqueous nasal solution (DDAVP rhinal tube) 0.1mg/ml; the starting dose is 0.05ml, as tablet form, the starting dose is 0.05mg, and as nasal puffs, the starting dose is 5mcg. All 5 endocrinologists who used desmopressin, they used it as subcutaneous injection or oral. Neonates who were given desmopressin responded to it with normalization of sodium level within 2-3 days. All neonates had fluctuating sodium level from 122 to 156mmo/L.

DISCUSSION

CDI is a rare disorder of water homeostasis that is characterized by excretion of large volumes of hypotonic urine either due to the defective production, transport or secretion of the hormone arginine vasopressin. CDI is caused by a variety of conditions (genetic, congenital, inflammatory, neoplastic, traumatic) that arise mainly from the hypothalamus [6]. The differential diagnosis between diseases presenting with polyuria and polydipsia is challenging and requires a detailed medical history, physical examination, biochemical approach, imaging studies and, in some cases, histologicalconfirmation. Magnetic resonance imaging is the gold standard method for evaluating the sellar-suprasellar region [6]. Early diagnosis and treatment are preferable in order to start treatment to avoid dehydration and electrolytes imbalance.

In this survey, we asked 35 pediatric endocrinologists to participate in their definition of diabetes insipidus and management. There was agreement that diabetes insipidus can be defined as a disease in which large volumes of dilute urine are excreted due to anti diuretic hormone deficiency and this is called central diabetes insipidus, vasopressin resistance called nephrogenic diabetes insipidus, or excessive water intake, called primary polydipsia. Polyuria is characterized by urine volume in excess of 2 L/m^2/24 h or ~150 mL/kg/24 h at birth, 100–110 mL/kg/24 h up to 2 years of age.

A retrospective study was performed to review etiologies that may be contributory to the development of NCDI and between age of 0-1 year showed that 18% had cerebral infarction, 27% had intracranial injury and hemorrhage due to traumatic brain injury, 18% had isolated intraventricular hemorrhage, and 27% had meningitis. Similarly, in our group, 26% of had intracranial hemorrhage and 31% had congenital anomalies.

There was an agreement among the pediatric endocrinologists in this survey that thiazide diuretics are safe and effective in infants and young children with NCDI and it can be continued after the introduction of solid food, and until a lack of response is observed. A study published few years back showed its efficacy for several months [8]. Ten of their 13 patients continued receiving thiazides after age 1 year with no significant side effects.

Neonates with NCDI on thiazide therapy usually do not need adjunctive treatment of hypercalcemia, which rarely occurs and usually resolves with thiazide dose reduction. Previously, poor weight gain was reported with thiazide-based regimens but was not reproduced in subsequent studies. Infants on thiazides show less variable sodium levels than do infants treated with desmopressin [8].

Five of the pediatric endocrinologists used desmopressin in this study and showed positive response. Three of them used subcutaneous desmopressin and 2 used oral.

A study assessed efficiency of oral desmopressin lyophilisate in 4 newborns with NCDI

presented with polyuria and hypernatremia which showed that oral desmopressin is practical and safe in the treatment of CDI during the first year of life. No episodes of hyponatremia were encountered. Weight gain and growth of the infants were normal during the mean follow-up duration [9, 10].

CONCLUSION

CDI is a rare pediatric endocrine disorder during neonatal period. Diagnosis is challenging and management is difficult. The therapeutic goals are primarily to reduce polyuria and to avoid dehydration so that the child will be able to grow adequately and maintain a normal life style. Desmopressin, although is the drug of choice for CDI therapy in general, however during neonatal period, fluid management with or without thiazide is preferred. It is necessary to provide inpatient care to these children especially those presenting with dehydration, hypernatremia and significant failure to thrive.

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