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CLINICAL QUIZ

Persistent hypoglycemic attacks during hemodialysis sessions in an infant with congenital nephrotic syndrome: Answers

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Answers

1. Uremia is typically associated with abnormal glucose metabolism. Impaired metabolism and impaired tissue sensitivity of insulin are largely responsible for the abnormal glucose metabolism and hyperglycemia in patients with end-stage kidney disease (ESKD) [1]. The development of spontaneous hypoglycemia is an unusual manifestation of disturbed glucose metabolism in chronic kidney disease (CKD) [2]. There are multiple factors that contribute to hypoglycemia in patients with CKD, including decreased caloric intake, reduced renal gluconeogenesis, impaired release of epinephrine as a counter-regulatory hormone, concurrent hepatic disease, and decreased metabolism of drugs that lead to reduction in the plasma glucose concentration [3]. Infections, low glycogen storage of infants, long hemodialysis (HD) sessions, metabolic diseases, carnitine deficiency, and deficiencies in growth hormone, cortisol, and rarely thyroid hormone may be the other reasons for hypoglycemia in patients receiving HD [4] (Table 1).
2. The difficulty is that clinical findings of adrenal insufficiency are similar to those of renal failure [5]. Early detection of adrenal insufficiency can be difficult due to non-specific signs and symptoms including general weakness, easy fatigability, weight loss, anorexia, nausea, vomiting, and unexplained fever [6].Unexplained sustained hypotension and persistent hypoglycemia in ESKD patients should alert the clinicians for adrenal insufficiency [5]. Hyperpigmentation, called as "bronzing," can be the first sign of Addison's disease. If present, this characteristic change in the skin color should arouse suspicion for the disease in uremic patients. Electrolyte disturbances, especially hyponatremia and hyperkalemia, and metabolic acidosis are other important findings particularly for primary adrenal insufficiency. However, it is not easy to distinguish these abnormalities in patients with ESKD as they may also arise from renal failure. In addition, a patient receiving dialysis with adrenal insufficiency may not show electrolyte imbalance and metabolic acidosis, which is corrected with dialysis solution [7]. This situation may make the diagnosis of adrenal insufficiency harder in patients treated with dialysis.
3. There are limited data about causes of adrenal insufficiency in pediatric HD patients. According to case reports of adult HD patients, the etiologies of adrenal insufficiency are tuberculosis, systemic AA-amyloidosis, usage of the drugs (like megestrol acetate) which suppress the hypothalamic-pituitary-adrenal axis, pituitary apoplexy or atrophy, isolated ACTH deficiency, history of unilateral adrenalectomy, and steroid withdrawal in rejected renal allografts [8–13]. An adult study has shown that the rate of adrenal insufficiency was 20% in hypotensive HD patients. Primary adrenal insufficiency was caused mainly by infectious (cytomegalovirus and tuberculosis), autoimmune, and unknown disorders, and the secondary form

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Table 1 Causes of hypoglycemia in hemodialysis

- Inborn error of metabolism
  - Glycogen storage diseases
  - Fatty acid oxidation disorders
  - Ketogenesis disorders
- Endocrine disorders
  - Hyperinsulinemia
  - Adrenal insufficiency
    - Steroidogenesis disorders
    - Adrenal damage
    - Peroxisomal disorders
    - Abnormal adrenal development
    - Adrenal unresponsiveness to ACTH
  - Growth hormone deficiency
- Chronic kidney disease/hemodialysis associated
  - Malnutrition (depleted glycogen stores)
  - Low alanine/glutamine blood concentration
  - Cessation of enteral feeding
  - Carnitine deficiency
  - Catheter-related infections
- Others
  - Sepsis, shock
  - Liver dysfunction
  - Medication (beta-blocker, salicylates, steroid withdrawal)

mostly by exogenous steroid intake in this patient population [5].

4. In our patient with congenital nephrotic syndrome (CNS), one of the potential causes of primary adrenal insufficiency might be adrenal damage secondary to sepsis. Another potential cause might be a genetic disease that can explain both conditions. Therefore, we analyzed all coding exons of *SGPL1*, which has recently been shown to be associated with the NPHS14. We found a homozygous variation (c.1079G>T; p.G360V) in *SGPL1* (NM_003901) with Sanger sequencing. Both healthy parents were heterozygous for the same variation. Minor allele frequency of the variation was < 0.01. In addition, in silico analyses predicted this variation as pathogenic (i.e., Sorting Intolerant From Tolerant (SIFT) (http://sift.jcvi.org): damaging; MutationTaster (http://www.mutationtaster.org): disease causing; *Poly*morphism *Phen*otyping v*2* (PolyPhen2) (http://genetics.bwh.harvard.edu/pph2/index.shtml): probably damaging). Taken together, we considered that this variation is the underlying genetic abnormality causing the phenotype observed in our patient.

Discussion

In the majority of cases, CNS is caused by genetic defects leading to disruption of the glomerular filtration barrier resulting in proteinuria, hypoproteinemia, and generalized edema. In our patient, CNS was caused by a homozygous mutation of *SGPL1* that can lead to an autosomal recessive form of steroid-resistant nephrotic syndrome (SRNS) involving multiple organ systems [14, 15].

SGPL1 mutation is the only genetic abnormality causing both adrenal insufficiency and nephrotic syndrome by the same molecular mechanism. Two recent studies published simultaneously by different research groups report that recessive mutations in *SGPL1*, which encodes sphingosine-1-phosphate (S1p) lyase, cause a syndromic form of the SRNS with adrenal insufficiency. *SGPL1* degrades the intracellular signaling molecule S1p, which has roles in the regulation of various physiological processes, including cell migration, survival, and differentiation [14, 15].

The majority of patients with *SGPL1* mutations present with progressive renal dysfunction associated with focal segmental glomerulosclerosis in infancy or early childhood, resulting in ESKD within a few years. Some infants present with primary adrenal insufficiency. There are also cases presenting with in utero hydrops and fetal demise. Hildebrandt and colleagues employed whole exome sequencing to investigate recessive causes of SRNS [15], identifying nine different recessive *SGPL1* mutations in seven families. Patients showed extrarenal manifestations of disease, including ichthyosis, immunodeficiency, and peripheral neurologic defects. Metherell and colleagues identified homozygous *SGPL1* mutations in 11 patients, 8 of whom presented SRNS between the ages 1.5 months and 5.5 ages. The functional part of the same study showed that *SGPL1* knock-out mice have altered expression of steroidogenic enzymes in adrenal glands and mild mesangial hypercellularity, glomerular hypertrophy, and fibrosis in kidneys [14]. Both groups have suggested that some patients with *SGPL1* mutations may not exhibit all features of the syndrome and the renal phenotype may exist as an isolated form [14, 15].

Adrenal insufficiency might be masked in these patients due to initial steroid treatment for the kidney disease. Our case presented with CNS and adrenal insufficiency. Her immunological workup was normal and there was no sign of ichthyosis.

Conclusion

NPHS14 due to *SGPL1* mutations should be kept in mind as an important differential diagnosis in patients with the coexistence of adrenal insufficiency and SRNS or CNS. Symptoms and signs of adrenal insufficiency are usually non-specific and can be masked by similar findings of renal failure. Early determination of adrenal insufficiency is important to avoid adrenal crisis, which can be a life-threatening condition. Recurrent hypoglycemia, unexplained hypotension,

hyperpigmentation, and hypercalcemia should warn the clinician for adrenal insufficiency in patients receiving HD.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

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