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Alagille Syndrome: An ultrafiltration dilemma

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ABSTRACT

Alagille syndrome (AGLS) is a rare genetic disorder caused by mutations in the Notch signaling pathway. Multiple organ dysfunction is frequent despite phenotypic variability. We report the case of an AGLS patient with right heart failure and persistent fluid overload who started peritoneal ultrafiltration, without initial benefit. Possible pathophysiological mechanisms related to the underlying genetic condition, namely vascular abnormalities, that could help explain the poor ultrafiltration are provided, while other ultrafiltration failure causes are briefly discussed. New evidence is necessary for a better understanding of this syndrome in PD modality.

Keywords: Alagille syndrome, JAG1 mutation, ultrafiltration, peritoneal dialysis.

INTRODUCTION

Alagille syndrome (ALGS) is an autosomal dominant multisystemic disorder, with variable phenotypic penetrance, caused by mutations in the Notch signaling pathway. The majority of patients (more than 90%) have a detectable mutation in JAG1, while a smaller percentage has mutations in NOTCH2[1]. The main pathological feature consists of hepatic involvement with chronic cholestasis due to paucity of intrahepatic bile ducts, but involvement of the heart, skeleton, eyes, kidneys, central nervous system and a wide variety of vascular abnormalities have also been reported[2]. Recent evidence suggests renal involvement is present in 39% of cases, with renal dysplasia being the most common manifestation (58.9%)[3]. Renal tubular acidosis, vesicoureteral reflux and urinary obstruction are other possible renal presentations. Chronic kidney disease (CKD) is common in ALGS[4], although renal insufficiency requiring renal replacement therapy is rare[5]. The paucity of available data in these patients with end-stage CKD leads to therapeutic dilemmas in clinical practice and demands careful evaluation and individualized decisions.

CASE REPORT

A 48-year-old female patient with ALGS diagnosed at age 30 (confirmed mutation in JAG1)[6] and CKD was admitted to our Nephrology Department with worsening congestive heart failure (HF), refractory to diuretic therapy. Progressive worsening of volume overload had developed in the preceding months, despite failed attempts of optimizing medical management with consecutive increments of furosemide (up to 240mg a day), causing poor symptom control and leading to several hospitalizations for intravenous therapy.

Clinical features of ALGS included dysmorphic facial features (prominent forehead, deep-set eyes, pointed and small chin and hypertelorism), chronic cholestasis and several vascular abnormalities, namely intracranial aneurisms, abdominal aortic and bilateral renal artery hypoplasia as well as pulmonary artery stenosis. This characteristic anomaly led to chronic and refractory right ventricular HF, which, together with the vascular renal hypoplasia, accounted for CKD and its progression.

A strategy of peritoneal ultrafiltration (PUF) was considered, assuming that a better fluid status and cardiorenal hemodynamics would improve her global clinical condition. After patient's consent, urgent-start PUF was initiated in an ambulatory setting, following proper training, with a single daily 2L exchange of isotonic icodextrin during 8 hours.

Upon re-evaluation, however, there was no evidence of symptomatic relief and PUF records showed insignificant ultrafiltration. Two additional exchanges with 2L of 2.27% glucose solutions during 4 hours each were added to the PUF scheme, without improvement in UF capacity and consequent failure of preventing weight gain. Plain abdomen X-ray showed adequate catheter location and there was no apparent obstruction to infusion or drainage. Clinical examination did not suggest peritoneal leaks or signs of peritonitis and laboratory workup excluded decrease in residual renal function (RRF). Patient adherence to fluid and salt restriction and to the PUF scheme was confirmed.

A peritoneal equilibration test (PET) was performed, showing a low transport profile (dialysate-to-plasma ratio of creatinine at 4 hours of 0.4). Dwell time was then increased to 7 hours between the two exchanges of 2.27% glucose solutions (icodextrin was temporarily

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suspended), with significant increase in net ultrafiltration (400-700mL/each exchange) and clinical improvement ensued. Six months after PUF introduction, there has been no need for new hospital admissions due to HF.

DISCUSSION

PD offers an alternative therapeutic option in refractory HF and reduces the incidence of decompensation. A systematic review[7] was recently conducted and included 14 prospective and 7 retrospective studies (n=673 patients), indicating a benefit in patients' symptoms, fluid balance, hospitalization rate and quality of life, despite no significant effect on overall survival[8]. Still poorly defined are the clinical characteristics of HF patients who may benefit most from PUF and the best protocols and procedures for delivering PUF. Management of these patients gets even trickier when daily net ultrafiltration is insufficient to maintain euvolemia, as in our case.

Various factors can alter the ability to control overhydration with PUF and nephrologists should conduct a complete workup into all possible etiologies. Our team excluded major causes of poor UF, including catheter-related mechanical or infectious complications, peritoneal leaks, lack of patient adherence and decrease in RRF. Highly effective peritoneal surface area (type 1 UF failure) was also set aside since this condition mainly occurs in long-term PD patients, dialysate-to-plasma (D/P) creatinine ratio > 0.81 is a hallmark and icodextrin has high potential to improve UF, which didn't happen in the present case. For similar reasons, inadequate water removal via aquaporins through decreased osmotic conductance (type 2 UF failure) was unlikely, as icodextrin solute and fluid transport relies predominantly on the small pore system[9] and we still experienced minimal UF with this solution. Fluid absorption from the peritoneal cavity into lymphatics (type 4 UF failure) is another cause to bear in mind and it has been suggested that icodextrin UF failure may be an indirect evidence for a high rate of fluid absorption from the peritoneal cavity[10]; in this case, though, ultrafiltration was reestablished after increasing dwell time.

ALGS is a rare cause of HF and, to the best of our knowledge, this is the first case report of PUF in this type of patients. This case is also impressive for the unusual renal involvement due to renal artery hypoplasia and cardiorenal syndrome secondary to pulmonary artery stenosis. Furthermore, the UF-resistant HF and slow transporter profile raises an important question: is there an ALGS-related intrinsic barrier to PUF?

The Notch family comprises a number of transmembrane proteins that interact as regulators of cell fate decisions and play an important role in vascular development and arteriovenous differentiation. It is also involved in mesenchymal-endothelial cell signaling that stabilizes the vasculature. A recent review further suggests that vasculopathy may explain the multisystemic phenotype of AGLS[11]. Considering vasculopathy is the primary abnormality in AGLS, it would be expected that clinical manifestations might be explained by abnormal vascular development, with theoretical extent to peritoneal microvasculature. One could, therefore, hypothesize that AGLS patients may have a low effective peritoneal surface area due to peritoneal vessel anomalies, even though others factors may contribute, including fibrosis induced by TGF-β[12].

CONCLUSION

To date, there is limited evidence for PUF in HF patients suffering from AGLS. Our case report showed an ultrafiltration-resistant patient with a low solute transport that, after excluding other causes of UF failure, demonstrated clinical improvement after increasing dwell time. We hope to raise awareness to a possible specific AGLS-related peritoneal microvasculature or membrane alteration caused by JAG1 or NOTCH2 mutations and to the need for future studies to confirm this hypothesis. Until new evidence comes to light, these patients warrant careful evaluation and individualized decisions.

Disclosure of potential conflicts of interest: none declared.

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