Journal of Pediatric Surgery 51 (2016) 794–797

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Prevalence of renal abnormality in pediatric intestinal failure☆

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ARTICLE INFO

Article history:
Received 24 January 2016
Accepted 7 February 2016

Key words:
Pediatric
Intestinal failure
Renal abnormality
Parenteral nutrition

ABSTRACT

Background: Outcomes of children with intestinal failure have improved over the last decade. However, with improved survival, other co-morbidities have become evident. The goal of our study was to evaluate the presence of renal nephrocalcinosis or increased echogenicity in a cohort of patients with pediatric intestinal failure (PIF).
Methods: A cross-sectional prevalence design was performed in PIF patients followed by our intestinal rehabilitation program between 2013 and 2014. Renal function was evaluated using serum creatinine and urea, urine oxalate, creatinine, calcium, and calcium/creatinine ratios. Renal ultrasounds were performed to assess for echogenicity. Data was collected on intestinal failure related factors and nutritional intake. Data was analyzed using medians and Mann–Whitney U or proportions and chi square.
Results: Fifty-four patients (median age 48 months; 33 males (61%) were studied. Twenty-two patients (41%) had increased echogenicity or nephrocalcinosis on ultrasound. There were no differences in serum Creatinine or urea, but patients with nephrocalcinosis had statistically different calcium:creatinine ratio (1.69 vs 0.74; $p = 0.043$), urine oxalate (108 vs 219; $p = 0.06$), and serum phosphate (1.55 vs 1.75; $p = 0.044$). Patients with echogenicity had a shorter colonic remnant (25 cm vs 31 cm; $p = 0.01$), a history of longer PN exposure (928 vs 483 days; $p = 0.05$), percent PN calories (37 vs 0; $p = 0.05$), PN h/day (13 vs 0; $p = 0.05$), but no difference in PN Ca/phosphate/magnesium content (mmol/kg).
Conclusion: A large proportion of PIF patients have increased echogenicity/nephrocalcinosis on ultrasound that is associated with prolonged PN exposure. This has implications for long-term management. Regular surveillance is required, and further study is warranted to determine specific risk factors.

Pediatric intestinal failure (PIF) is defined as the inability of the gastrointestinal tract to sustain life without supplementation with parenteral nutrition (PN) [1]. The most common cause of intestinal failure (IF) is short bowel syndrome (SBS) with an overall incidence of 22.1 per 1000 neonatal intensive care admissions and 24.5 per 100,000 live births [2]. Mortality rates within PIF are estimated to be around 30% [3–5], but vary greatly depending on age at diagnosis and underlying disease. Introduction of multidisciplinary teams and novel therapies have resulted in improved outcomes, but children with IF remain at risk for multiple co-morbidities, including liver dysfunction, electrolyte imbalance, metabolic bone disease, and infectious complications [2–5].

Patients with irreversible IF require PN for maintenance of fluid, electrolyte and protein-energy balance. Patients require long-term PN until intestinal adaptation occurs or serious complications arise necessitating intestinal transplantation [3,4]. Renal dysfunction was first reported by Moukarzel et al. in 1991 in children receiving long-term PN. They reported a decrease in glomerular filtration rate (GFR) but were unable to identify a contributing mechanism [6]. Reports in adult patients on long-term PN have suggested that 50% of patients had decreased renal function characterized by a decreased GFR or progressive decrease of GFR [7–9]. A recent retrospective cross-sectional study compared the prevalence of chronic kidney disease (CKD) between adults on PN versus intestinal transplant (ITx). It found that while ITx patients have a significant risk for developing CKD, patients on long-term PN showed an annual estimated GFR (eGFR) decline of 2.8% and after a median duration of 7 years of PN a prevalence of mild CRF in 21.2% [10]. The mechanism for the decline in renal impairment has not been identified in previous studies [8–10].

Abbreviations: IF, intestinal failure; PN, parenteral nutrition; SBS, short bowel syndrome; PIF, pediatric intestinal failure; GFR, glomerular filtration rate; CKD, chronic kidney disease; ITx, intestinal transplant; eGFR, estimated glomerular filtration rate; TFI, total fluid intake; IQR, interquartile range; RR, relative risk; US, ultrasound; SB, small bowel; LB, large bowel; cm, centimeter.

☆ Level of Evidence: 3.

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http://dx.doi.org/10.1016/j.jpedsurg.2016.02.025
0022-3468/

It is well recognized that creatinine is a poor marker for renal function, especially in the early stages of renal damage. Increased echogenicity of the renal parenchyma on renal ultrasound is a non-specific finding but is usually indicative of renal parenchymal disease, outside the newborn period where the kidneys are routinely echogenic. The causes of increased renal echogenicity are multiple and include glomerular disease, tubular disorders and interstitial inflammation, and nephrocalcinosis. Findings of increased echogenicity on ultrasound (US) though nonspecific are an important finding and may signify the presence of renal disease [11,12]. Nephrocalcinosis is defined as mineral precipitates within the renal parenchyma [13]. The formation of nephrocalcinosis is often a result of an imbalance between stone-promoting and stone-inhibiting factors and is often multifactorial. Factors that can lead to the promotion of nephrocalcinosis include acidosis, medications such as diuretics and vitamin D supplementation, hyperoxaluria, PN, fat malabsorption, episodes of dehydration [14,15]; all of which exist in PIF patients.

An index child with PIF was noted to have severe nephrocalcinosis, and several patients were reported to have abnormal renal echogenicity on renal ultrasound. This prompted us to look at renal function and the prevalence of nephrocalcinosis and/or abnormal renal echogenicity in our PIF population to try and identify risk factors for the later development of CKD in this cohort.

The goals of our study were to evaluate the prevalence of renal abnormality in a cohort of pediatric patients with IF and identify factors associated with its development.

1. Methods

We performed a retrospective cross-sectional prevalence study to determine the proportion of patients with nephrocalcinosis and/or abnormal renal echogenicity. Pediatric intestinal failure patients managed by our multi-disciplinary intestinal rehabilitation program at The Hospital for Sick Children in Toronto during 2013–2014 were potential candidates. Patients had a history of prolonged PN use but did not have to be on PN at the time of evaluation. Patients receive regular monitoring and follow-up for PN related complications which includes yearly vascular ultrasound, abdominal ultrasound and DEXA scans. Patients who did not receive an abdominal/renal ultrasound completed during the study period were excluded. In addition, patients with previous liver or intestinal transplantation were not included in analysis.

Data was collected from the electronic patient chart. Demographic data collected included date of birth, gestational age (weeks), gender, etiology of IF, category of IF (SBS, mucosal enteropathy or primary dysmotility). Residual intestinal anatomy including both absolute length and percentage of expected length based on established norms [16] of both small and large bowel was recorded. In addition, presence of an ostomy and presence of the ileocecal valve were included. To quantify PN exposure, we collected total number of PN days, percentage of PN calorie support, number of PN infusion hours per day, and total fluid intake (TFI) per kilogram per day. PN composition was also collected and included amount of prescribed acetate, calcium, phosphate and magnesium.

Laboratory values collected included spot urinary calcium, chloride, creatinine, sodium, citrate, and oxalate. Serum biochemistry data included creatinine, ionized calcium, phosphate, urea, 25-hydroxy vitamin D level and serum blood gas. Based on urine biochemical values, calculations were completed to determine the calcium:creatinine ratio, calcium:citrate ratio and citrate:creatinine ratio. Radiology results for abdominal/renal ultrasounds were collected to determine the presence of nephrocalcinosis or echogenicity. Kidney length was also recorded. All laboratory results had to be drawn within two months of the completion of the renal ultrasound to be included in the analysis. All data collection was completed by two clinical nurse practitioners with extensive clinical experience. Reference ranges for renal values were obtained from several sources to provide parameters and age ranges [17–20].

Patients were stratified based on the presence of nephrocalcinosis or increased echogenicity on renal ultrasound. Baseline and outcome data were compared using appropriate summary statistics. Continuous variables were presented as medians with interquartile range (IQR) as the data was not normally distributed after review of frequency histograms. Data was analyzed using the Mann–Whitney *U* test. Categorical variables were presented as frequencies and proportions and statistical testing was performed with the chi square. Relative risks (RR) were included as a measure of association. An alpha-value of 0.05 was considered statistically significant. IBM SPSS Statistics 22 (2013) was used for the analyses.

2. Results

During the study enrollment period, fifty-six patients met inclusion criteria with a median age of 48 months and 35 patients were male (57%). Of the participants 24 (43%) had increased echogenicity or nephrocalcinosis on US compared to 32 participants without radiographic evidence of renal abnormality.

Table 1 displays the patient characteristics based on presence of echogenicity and nephrocalcinosis at the time of ultrasound. The majority of patients had SBS (73.9% for nephrocalcinosis/echogenicity and 81.3% for no-nephrocalcinosis/echogenicity, respectively). Residual small bowel length did not differ significantly between the two groups; however, the colonic remnant was significantly shorter in the group with renal impairment ($p = 0.001$). PIF patients with renal abnormality on US were also more likely to have a stoma (70.8% vs 45.2%; $p = 0.05$; RR = 1.9, 95% CI 1.0–3.7).

Table 2 illustrates the impact of PN exposure and composition on development of nephrocalcinosis/echogenicity. The total exposure to PN in days was significantly more in PIF patients with nephrocalcinosis/echogenicity (928 vs 500; $p = 0.05$), as was the percentage of total calorie delivery in the form of PN (37% vs 0%; $p = 0.05$) and PN TFI [in ml/kg/day] (103 vs 21; $p = 0.05$). The number of PN infusion hours per day was not significantly different between the two groups (13 vs 4; $p = 0.102$). The number of PIF patients receiving PN at the time of renal US was higher in the nephrocalcinosis/echogenicity group (70.8% vs 43.8%; $p = 0.044$) with a relative risk of 2.0 (95% CI 1.0–3.9). Parenteral nutrition composition was compared between the two groups for calcium, phosphate, magnesium and acetate (mmol/kg/day). The composition of the parenteral nutrition did not vary between the two groups.

Serum and urine biochemistry results for the two groups are displayed in Table 3. At the time of measurement urinary calcium was

Table 1
Patient characteristics.

	Nephrocalcinosis/ echogenicity (n = 24)	Normal (n = 32)	P-value
Age (months)	48 (21–82)	27 (16–62)	0.362
Male (%)	17 (70.8)	18 (56.3)	0.403
Gestational Age (weeks)	35 (32–40)	35 (33–38)	0.811
IF Category (%)			0.373
SBS	17 (73.9)	26 (81.3)	
Enteropathy	1 (4.3)	3 (9.4)	
Dysmotility	5 (21.7)	3 (9.4)	
Residual SB length (cm)	45 (25–100)	64 (19–133)	0.519
Residual SB %	27 (14–66)	45 (15–100)	0.361
Residual LB length (cm)	25 (15–35)	33 (30–40)	0.007
Residual LB %	50 (30–90)	100 (75–100)	0.001
Stoma Present (%)	17 (70.8)	14 (45.2)	0.05
On PN at time of US (%)	17 (70.8)	14 (43.8)	0.04

Values are medians with interquartile ranges.
% represents frequencies and percentages.
IF = intestinal failure; SBS = short bowel syndrome; SB = small bowel; LB = large bowel; PN = parenteral nutrition; US = ultrasound.