Practical pediatric nephrology

Gastrointestinal function in chronic renal failure

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Abstract. Feeding problems, anorexia and vomiting are common in infants and children with chronic renal failure (CRF), and play a major role in the growth failure often found in this condition. However, the gastroenterological and nutritional aspects of CRF in children have received little attention, hence therapeutic interventions are usually empirical and often ineffective. Gastritis, duodenitis and peptic ulcer are often found in adults with CRF on regular haemodialysis and following renal transplantation. Despite persistent hypergastrinaemia, gastric acid secretion is decreased rather than increased in most of these patients, and active peptic disease appears to be promoted by the removal of the acid output inhibition (neutralisation of gastric acid by ammonia) that follows active treatment. Helicobacter pylori, on the other hand, does not seem to play a significant role in the pathogenesis of peptic disease in CRF. Gastro-oesophageal reflux has been found in about 70% of infants and children with CRF suffering from vomiting and feeding problems, and thus appears to be a major problem in these patients. In a number of symptomatic patients with CRF, gastric dysrhythmias and delayed gastric emptying have also been found; hence there appears to be a complex disorder of gastrointestinal motility in CRF. Serum levels of several polypeptide hormones involved in the modulation of gastrointestinal motility [e.g. gastrin, cholecystokinin (CCK), neurotensin] and the regulation of hunger and satiety [e.g. glucagon, CCK] are significantly raised as a consequence of renal insufficiency, and can be reverted to normal by renal transplantation. Furthermore, several other humoral abnormalities (e.g. hypercalcaemia, hypokalaemia, acidosis, etc.) are not uncommon in CRF. By directly affecting the smooth muscle of the gut or stimulating particular areas within the central nervous system, all these humoral alterations may well play a major role in the gastrointestinal dysmotility, anorexia, nausea and vomiting in patients with CRF. Specific pharmacological and nutritional interventions should thus be considered for the treatment of vomiting and feeding problems in CRF.

Key words: Chronic renal failure – Anorexia – Vomiting – Gastrointestinal function – Polypeptide hormones

Introduction

Growth impairment is a major problem in children with chronic renal failure (CRF). Growth retardation is already present in more than half of the children when renal failure is first diagnosed, especially if the renal impairment began in the 1st year of life, when growth is most rapid [1, 2]. It is widely accepted that in infants and children with CRF growth may be influenced by a number of different factors, including metabolic acidosis, anaemia, hypertension, renal osteodystrophy, water and electrolyte imbalance and endocrine abnormalities [1, 2]. Moreover, the meticulous management of acid-base and electrolyte balance, bone disease and anaemia may improve growth in most of these children, especially when they are treated early [1–3]. Furthermore, the definitive correction of these abnormalities by renal transplantation results in a significant increase in growth velocity [4].

In addition to the problems mentioned above, infants and children with CRF very often suffer from recurrent vomiting, anorexia and feeding problems. The reduced intake of calories resulting from these symptoms is a major determinant of their poor growth [1, 2, 5], and it has been clearly shown that careful nutritional management and adequate caloric supplementation by enteral feeding may induce significant catch-up growth in children with CRF who are failing to thrive [2, 5]. Anorexia and upper gastrointestinal symptoms, such as regurgitation, nausea, vomiting, bloating and early satiety, are commonly reported also by adult uraemic patients [6], in whom they can contribute to undernutrition and poor quality of life.

As anorexia and vomiting pose relevant problems for both the patients and the carer, their aetiology, pathogenesis and management deserve attention. However, little research
has been performed on the gastroenterological aspects of CRF in infancy and childhood, whereas there are a number of papers in adult patients. The aim of this article is to review the currently available information on the involvement of the gastrointestinal tract and its relationship with anorexia, vomiting and feeding problems in infants and children with CRF. Four major areas of interest can be identified: (1) mucosal lesions and acid secretion (these two aspects have often been studied together), (2) exocrine pancreas, (3) gastrointestinal motility and (4) regulatory peptides.

**Mucosal lesions and gastric acid secretion**

Gastroduodenal inflammation is very common in adult patients with CRF on haemodialysis, occurring in 25%–67% of cases [6–9]. Antral gastritis is the lesion most commonly found, with a prevalence of about 50%, whereas duodenitis is slightly less frequent, with a prevalence of 9%–43% [6–10]. In contrast, active peptic ulcer does not appear to be more common in patients on haemodialysis than in the general population [8, 10], but the frequency of gastrointestinal complications, notably haemorrhagic gastritis and peptic ulcer, increases after active treatment [7, 8, 10]. As patients with CRF have a persistent hypergastrinaemia [11], it was assumed that they had hypersecretion of gastric acid, which in turn might cause gastroduodenal peptic disease. However, despite an increased density of gastric parietal, chief and G-cells in CRF, gastric acid secretion is usually decreased rather than increased, most likely due to the neutralisation of gastric acid by ammonia (acid output inhibition) [10, 12]. These observations suggest that the hypergastrinaemia is not only a consequence of the reduced renal clearance of gastrin, but is also compensatory, i.e. secondary to the decreased acid output. Thus, the presence and severity of gastroduodenal complications are not consistently related to the serum gastrin levels and the amount of acid secretion, nor are they related to the degree of renal insufficiency [10, 12]. The removal of acid output inhibition that follows regular haemodialysis and successful renal transplantation would then explain the increased frequency and severity of gastroduodenal peptic disease after active treatment [10, 12].

The risk of gastrointestinal bleeding is higher in patients on haemodialysis who have angiodyplastic lesions of the digestive tract, especially when hypertension, congestive cardiac failure, diabetes mellitus or coronary artery disease are present [13]. However, mucosal cytoprotection does not seem to be affected by CRF, as the levels of prostaglandin E2 in the gastric mucosa (normal, inflamed, atrophic and ulcerated) are similar in subjects with CRF and subjects without renal disease [14].

*Helicobacter pylori*, a Gram-negative bacterium considered the most common causative agent of antral gastritis and duodenal ulcer [15], could theoretically be implicated in most of the gastrointestinal inflammations and ulceration seen in CRF. As *H. pylori* produces urease, the high gastric juice urea levels in CRF might create a favourable (i.e. selective) environment for its growth. The few studies carried out so far, however, do not support this hypothesis. Firstly, in adults with CRF the prevalence of *H. pylori* is similar to that of healthy controls, irrespective of the presence of upper gastrointestinal symptoms [16, 17], and does not differ between patients on haemodialysis and patients who have undergone transplantation [18]. Secondly, patients with CRF on maintenance dialysis have a relatively low prevalence of duodenal colonisation by *H. pylori* despite a high incidence of gastric metaplasia, which predisposes to *H. pylori* colonisation [19]. Thirdly, although *H. pylori* is associated with active antral gastritis and dyspeptic symptoms in a number of patients with CRF, its prevalence is much (about 50%) lower than in patients with duodenal ulcer, and is unrelated to plasma urea and gastric acid secretion [16]. Thus, there is no firm evidence of a predisposition to *H. pylori* infection in CRF, nor does *H. pylori* seem to play a major role in the peptic ulcer disease of patients with CRF. The clinical significance of gastrointestinal peptic disease in CRF is not clear, as upper gastrointestinal complaints were reported by many patients with CRF in whom no macroscopic or histological lesions could be found on upper gastrointestinal endoscopy or X-ray [6, 17]. To date, no data have been published on the prevalence of gastroduodenal inflammation and ulceration and the prevalence of *H. pylori* in children with CRF. However, studies in adults suggest that gastrointestinal colonisation by *H. pylori* is uncommon; therefore *H. pylori* is not particularly relevant for the pathogenesis of gastrointestinal symptoms in infants and children with CRF.

**Exocrine pancreas**

The exocrine pancreas is frequently involved in CRF. Attacks of symptomatic acute pancreatitis have been radiologically documented in patients with end-stage renal disease, particularly in those on haemodialysis [20]. Histological evidence of pancreatitis and many other alterations (ductal ectasia, ductular proliferation, cystic changes, amyloidosis, abscess formation, etc.) were found in varying proportions of patients: from 45% in the pre-dialysis era to 71% on maintenance haemodialysis [21–23]. This increasing prevalence of pancreatic damage is probably related to prolonged patient survival, as well as iatrogenic factors (haemodialysis procedures, steroids and other immunosuppressive drugs, etc.). The clinical significance of such morphological changes is unclear, as they were not usually associated with relevant symptoms. However, pancreatic enzyme supplementation has been beneficial in a few patients with end-stage renal disease [24]. The aetiology and pathogenetic mechanisms of uremic pancreatic disease are also unclear. Experimental studies in nephrectomised rats showed that the early morphological and biochemical changes are similar to those seen in alcohol-induced pancreatic disease and other types of toxic pancreatic damage, and are characterised by acinar cell depletion, increased cellular turnover and a progressively decreasing secretory response [25–27]. To explain all the abnormalities of uremic pancreopathy, a multifactorial pathophysiological scheme has been proposed which incorporates: (1) the role of secondary hyperparathyroidism (excess ionic calcium inducing accelerated conversion of