

positive for both IgG anti-HHV-6 (1:160) and IgM anti-HHV-6 (1:80). A maculopapular rash appeared over her face, scalp, and neck on the fourth day of illness. She became afebrile soon after the rash eruption. No sequela was noted one month after discharge.

CASE 2

This 4 month old boy presented with cough, poor appetite, and high fever. Four episodes of generalised seizure occurred in the next two days with persistent fever. Examination of his cerebrospinal fluid performed on the third day of illness revealed 8 polymorphonuclear cells and 1 mononuclear cell/mm³. Cerebrospinal fluid protein and glucose concentrations were normal. A peripheral blood smear revealed lymphocytosis (total white cell count was $9.6 \times 10^9/l$, lymphocyte 73%, and atypical lymphocyte 6%). Impaired liver function was noted (aspartate aminotransferase 87 U/l and alanine aminotransferase 50 U/l. His electroencephalogram was normal. A diffuse maculopapular rash appeared over his trunk and lower extremities on the fourth day of illness and his fever soon subsided. Virus culture of throat swab, rectal swab, and cerebrospinal fluid showed no pathogens. The first serum taken on the fifth day of illness was negative for both IgG and IgM anti-HHV-6. The second serum taken 12 days later was positive for both IgG anti-HHV-6 (1:160) and IgM anti-HHV-6 (1:40). The boy recovered well and no sequela was noted two months later.

Discussion

Both cases underwent a typical course of roseola infantum, that is, high fever for three to four days' duration followed by skin rash eruption and lysis of fever and recovery. Case 1 was neurologically normal and case 2 suffered from repeated seizures. Both had pleocytosis and recovered well. HHV-6 has been known to infect glioblastoma cells² and is thought to be a potential cause of nervous system disease. Before the identification of HHV-6 in the aetiology of roseola infantum, encephalitis has been known to occur after roseola infantum.⁵

However, the connection between HHV-6 and these reported cases of encephalitis was not certain as no study on HHV-6 was done and enterovirus was incriminated as a possible aetiological factor as it may cause a roseola-like disease. Although the number of diseases linked to HHV-6 are increasing, the connection of HHV-6 with nervous system illness has been shown only by Irving *et al* who reported a 13 month old girl suffering from encephalitis and experiencing brain atrophy six months later.⁶

Our cases had serological evidence of acute primary HHV-6 infection and a search for other viruses failed. Both cases had lymphocytosis and a certain degree of atypical lymphocytosis; one of them fulfilled the diagnosis of mononucleosis syndrome. From the clinical information we believe that HHV-6 was responsible for the full clinical features of these two children.

Roseola infantum is, in a paediatrician's mind, a benign disease. Seizure is not uncommon and is mostly attributed to a febrile convulsion. Though both our cases experienced mild neurological insults, there is no guarantee that HHV-6 causes only mild nervous system disease. Testing for HHV-6 in unexplained neurological inflammatory diseases is therefore important, especially in infants. An additional point is the occurrence of mononucleosis and hepatitis that we observed; both have been reported before.^{2,3} This finding supports the view that HHV-6 is capable of causing a variety of illnesses.

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Severe nephropathy in three adolescents with cystic fibrosis

M L Melzi, D Costantini, M Giani, A Claris Appiani, A M Giunta

Abstract

Renal involvement has rarely been reported in patients with cystic fibrosis. We describe severe nephropathy with a rapidly fatal outcome in three adolescents with cystic fibrosis, and evaluate the important repercussions that the nephrotic syndrome had on the precarious clinical situation of these patients.

Despite the general consensus that the kidney is spared in cystic fibrosis and does not present specific lesions, mounting evidence suggests that renal involvement occurs. Numerous and even severe anatomical and pathological changes have been reported in the kidney in patients with cystic fibrosis.^{1,2} Glomerular alterations were seen (amyloidosis, glomerulosclerosis, mesangial deposits of immuno-

Department of
Paediatrics,
University of Milan,
Italy

M L Melzi
D Costantini
M Giani
A Claris Appiani
A M Giunta

Correspondence to:
Dr Maria Luisa Melzi,
Via Commedia 9,
20122 Milano,
Italy.

Accepted 25 July 1991
(*Arch Dis Child* 1991;66:1444-7)

globulins and/or immune complexes, and mesangial proliferation) and also some tubular changes (lymphoplasmacytic infiltrations, fibrosis, and tubular atrophy). Microscopic nephrocalcinosis with intratubular, peritubular, and intracellular deposits has recently been described in cystic fibrosis patients, including very young children (under 1 year).

In contrast to the numerous anatomical and pathological reports, clinical data are scanty. In this paper we describe severe nephropathy with a rapidly fatal outcome in three adolescents and evaluate the unfavourable repercussions of the nephropathy on the precarious condition of these patients.

Patients and methods

Three non-diabetic patients with a late diagnosis of cystic fibrosis were followed up because of persistent proteinuria. They all underwent percutaneous renal biopsy under urographic guidance.

Specimens for light microscopy were fixed in Bouin's solution, embedded in paraffin, cut into sections of 2–3 μm and stained routinely with haematoxylin and eosin, periodic acid Schiff, and trichrome. Congo red staining was also done when amyloidosis was suspected. Specimens for immunofluorescence were tested with antisera monospecific for IgG, IgA, IgM, C3, C4, C1q, and fibrinogen.

CASE 1

This boy, the second child of healthy, non-consanguineous parents, presented with numerous episodes of bronchopulmonary infections from the first year of life. Cystic fibrosis was diagnosed when the boy was 7 years old, and at the age of 14 he was referred to our centre. He was then in a poor clinical condition. Growth was retarded, and there was respiratory impairment and poor cardiac function. A chest radiograph revealed marked changes consistent with cystic fibrosis. Sputum was colonised by staphylococci, pseudomonas, and candida. Renal function indices were normal (serum creatinine concentration $66.3 \mu\text{mol/l}$, blood urea nitrogen 7 mmol/l , creatinine clearance $108 \text{ ml/min/1.73 m}^2$, and normal urinalysis).

One year later a selective mild proteinuria ($0.5\text{--}1.0 \text{ g/day}$) appeared, which worsened in subsequent months, with a daily protein loss of up to 3 g. The next year a renal biopsy specimen revealed renal amyloidosis. Deposits positive for Congo red were observed at both glomerular and periarterial sites. The appearance of proteinuria was accompanied by a mild impairment of glomerular filtration (serum creatinine $114.9 \mu\text{mol/l}$, blood urea nitrogen 14 mmol/l , creatinine clearance $63 \text{ ml/min/1.73 m}^2$) and occasional alterations of blood pressure values (systolic pressure up to 140 mm Hg, diastolic pressure up to 110 mm Hg). In the months after biopsy proteinuria worsened, with values stabilised in the nephrotic range, and a nephrotic syndrome and haematuria appeared. At the same time renal failure became progressively more severe (fig 1), reaching the end stage and

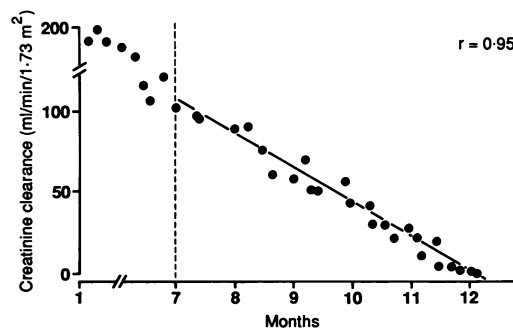


Figure 1 Pattern of glomerular filtration with amyloidosis (patient 1).

requiring dialysis the next year. The patient's clinical condition deteriorated rapidly, with severe respiratory impairment, altered fluid and electrolyte balance, poor cardiac function, and severe weight loss. Fifteen days after starting dialysis treatment the patient died of heart failure.

CASE 2

This girl was the firstborn child of healthy, non-consanguineous parents, and from the first months of life had frequent respiratory infections. At the age of 11.6 years the diagnosis of cystic fibrosis was made (sweat test chloride concentration, 97.3 mmol/l). Her clinical condition appeared fairly good (weight, 10th centile; height, 25th centile). Moderate clubbing was observed. A chest radiograph revealed important pulmonary impairment. The electrocardiograph was within normal limits. Moderate alterations were found in respiratory function tests. The coefficient of fat absorption was 47%. Sputum was colonised by staphylococci and pseudomonas.

Over the next four years respiratory function worsened slowly, acute pulmonary exacerbations were frequent, and episodes of haemoptysis occurred.

Renal function indices, investigated when the girl was 17.5 years, were within the normal range (serum creatinine concentration $75.1 \mu\text{mol/l}$, blood urea nitrogen 7.7 mmol/l , creatinine clearance $113.4 \text{ ml/min/1.73 m}^2$, no abnormalities at urinalysis). Some months later mild and occasional proteinuria ($0.5\text{--}0.7 \text{ g/day}$) was observed which during the course of a year worsened to a proteinuria in the nephrotic range (over 6 g/day), non-selective, without alteration of creatinine clearance, haematuria, or hypertension. A renal biopsy specimen, performed when the girl was 18.8 years, demonstrated a typical picture of renal amyloidosis. The sample did not contain glomeruli but amyloid deposits could be seen in the interstitium, particularly at peritubular sites.

After the development of the nephrotic syndrome there was a clear worsening of the clinical condition and nutritional status of the patient. In particular, severe infections were more frequent, it was extremely difficult to maintain fluid, electrolyte, and acid-base balances, and the cardiac condition deteriorated, with subsequent development of severe cardio-

pulmonary failure. Blood pressure and renal function indices remained normal. The girl died at the age of 18.9 years of heart failure.

CASE 3

This girl was the fourth child of healthy, non-consanguineous parents. In her first few years her symptoms were mainly gastrointestinal, and at the age of 6 years cystic fibrosis was diagnosed (sweat test chloride concentration, 98 mmol/l). The patient was referred to us at age 12 years in a very poor general condition. Chronic cor pulmonale, cyanosis, and clubbing were present, as well as dependent oedema for about 10 days. Growth was retarded. Major pulmonary impairment was shown at radiological examination. Sputum was colonised by pseudomonas and streptococci.

From the first investigations moderate proteinuria (about 1 g/day) was observed, without nephrotic syndrome. Proteinuria was accompanied by haematuria and renal function was not impaired (serum creatinine 40.7 $\mu\text{mol/l}$, blood urea nitrogen 8.8 mmol/l, creatinine clearance 86 ml/min/1.73 m²). A renal biopsy specimen showed a typical IgA nephropathy by immunofluorescence. Light microscopy revealed a picture of focal proliferative glomerulonephritis with crescents in 10% of the glomeruli.

For three years proteinuria remained at around 1 g/day, accompanied by occasional haematuria and with renal function indices in the normal range. When the patient was 15.3 years her proteinuria, which was non-selective, became rapidly more severe, reaching concentrations of 10 g/day, with haematuria still present and normal renal function indices. A nephrotic syndrome manifested quickly. The girl's general condition deteriorated with considerable worsening of cardiopulmonary function, a severe weight loss, and blood gas analysis showing respiratory acidosis. She developed hyponatraemia, hypokalaemia, and hypochloraemia. Renal function was normal until a few days before the patient's death when a rise occurred in serum creatinine (106.1 $\mu\text{mol/l}$) and blood urea nitrogen (34.3 mmol/l). She died of heart failure at the age of 15.4 years.

Figure 2 summarises the pattern of proteinuria in the three patients from its onset.

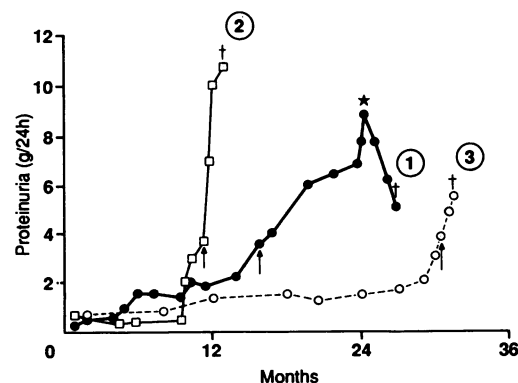


Figure 2 Pattern of proteinuria with amyloidosis (patients 1 and 2) and with IgA nephropathy (patient 3). † Death; * renal failure; the arrows indicate nephrotic syndrome.

Discussion

We observed three non-diabetic adolescents with cystic fibrosis who presented severe nephropathy that started as occasional mild proteinuria and evolved rapidly into nephrotic syndrome, with impaired renal function up to end stage renal failure in one patient. The outcome was fatal in all three patients, with deteriorating clinical condition, metabolic and nutritional imbalance, and increased susceptibility to infection.

Although anatomical and pathological changes may be present in the kidneys very early in subjects with cystic fibrosis, several years probably pass before precise clinical manifestations occur, so that nephropathy develops more often in adolescence, as our experience seems to suggest. In all of our cases the diagnosis of cystic fibrosis was made late, thus treatment of infections in their first years of life was probably inadequate. Moreover, the course of nephrotic syndrome in our patients was rapidly unfavourable, and had a devastating impact on their precarious metabolic, nutritional, cardiocirculatory, fluid, and electrolyte balances and on their blood gases. Histological examinations revealed renal amyloidosis in two of them (cases 1 and 2) and IgA nephropathy in one (case 3).

Systemic amyloidosis with renal involvement has been reported in some patients with cystic fibrosis.^{3,4} Secondary amyloidosis is in fact a complication of chronic inflammatory processes such as tuberculosis and bronchiectasis, and it is conceivable that this condition may develop in patients with cystic fibrosis which is characterised by chronic and recurrent respiratory infections. Necropsy was not performed in any of our patients, and thus the possibility that not only the kidney but also other organs such as the heart or liver might have been involved in the amyloid process cannot be excluded. However, radiographs did not demonstrate cardiomegaly in any of the cases, no signs of arrhythmia were revealed by electrocardiographs, and liver function as shown by biochemical data seemed unimpaired.

Experimental models⁵ and clinical observations⁶ indicate that circulating immune complexes containing IgA have an important pathogenetic role in IgA nephropathy. Patients with cystic fibrosis often have raised immunoglobulin concentrations, especially of the IgG class, related to frequent immune stimulation by recurrent bacterial infections. The role of the underlying disease in the development of IgA nephropathy in patient 3 is not clear. IgA nephropathy is a common type of glomerulonephritis and it is possible that this was just a chance association. Renal biopsy was done three years before the patient became nephrotic and she may have developed amyloid by the time she died.

The overall treatment (chest physiotherapy, nutritional support, and antibiotics) now given to subjects with cystic fibrosis from the time of diagnosis, which is often made in neonatal age or before the appearance of symptoms of the disease, has notably increased the life expectancy of these children, and thus also the

possibility of lung or heart and lung transplants in adequately selected cases. The selection of candidates for the transplant programme is crucial for their long term survival, and should include careful monitoring of renal function and signs of renal damage, particularly proteinuria. The patients now admitted to transplant programmes are generally in advanced stages of the disease when secondary complications are more probable. It is very important to exclude the presence of amyloidosis in these subjects. In our opinion, even the mild and occasional proteinuria that is sometimes observed in cystic fibrosis children merits particular attention, with the aim of promptly identifying patients at risk of progressively severe renal impairment and of

prescribing appropriate treatments to prevent or at least delay severe clinical manifestations.

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Nutritional manipulation in the management of dumping syndrome

Vikram Khoshoo, Ram M Reifen, Ben D Gold, Philip M Sherman, Paul B Pencharz

Abstract

Two children with Nissen's fundoplication and either gastrectomy or pyloroplasty developed dumping syndrome. Correction of their blood glucose abnormalities, resolution of symptoms, and weight gain were effectively achieved by addition of fats and uncooked corn starch (50 g/l) to their feeds.

There is a paucity of literature regarding the prevalence and optimal management of dumping syndrome in children. This results from the rapid gastric emptying of a carbohydrate meal, causing hyperglycaemia followed by reactive, symptomatic hypoglycaemia. Dumping syndrome in children has been described almost exclusively as a postoperative complication of Nissen's fundoplication.¹⁻³ Several therapeutic approaches have been tried with mixed results: for example, continuous nasogastric or gastrostomy feeds, frequent small amounts of thickened feeds and the addition of complex carbohydrates such as fibre and uncooked corn starch.^{4,5} We report on two children treated by a combination of complex carbohydrate and fats to delay gastric emptying and provide a stable release of glucose, leading to normoglycaemia and amelioration of symptoms.

Case reports

CASE 1

At 10 months of age this girl underwent bladder augmentation using gastric mucosa (that is, gastrectomy) for treatment of reflux nephropathy. At 15 months of age she had further bladder augmentation with ileocystoplasty and an antireflux procedure (Nissen's fundoplication) for clinically and radiologically significant gastro-oesophageal reflux. At 17

months (two months after surgery) she was readmitted for evaluation of persisting diarrhoea and food aversion. On specific questioning her parents reported that she also had acute abdominal discomfort and lethargy after meals, accompanied by pallor and sweating.

In hospital, a brief tonic-clonic seizure occurred postprandially. At that time she was found to be hypoglycaemic (1.5 mmol/l) and required correction with a glucose infusion. No other metabolic abnormality was detected. A computed tomographic scan of the brain and an electroencephalogram were both normal. Subsequently, in the hospital, an oral glucose tolerance test (2 g/kg glucose) was performed which showed an initial hyperglycaemic response (blood glucose concentration, 7.8 mmol/l at 30 min) followed by hypoglycaemia (blood glucose 3.5 and 2.1 mmol/l at 45 and 60 min, respectively). Barium swallow showed a normal oesophagus, microgastria, and rapid stomach emptying. The latter was confirmed by a gastric emptying scan with ^{99m}Tc-labelled sulphur colloid which showed no gastric residue at 30 minutes. A diagnosis of dumping syndrome was made and she was placed on frequent small feeds and the addition of corn oil. This alleviated the postprandial glucose abnormalities totally and clinical symptoms partially.

Two months later she was readmitted for continued symptoms relating to the dumping syndrome, including irritability, worsening food aversion, and slow weight gain. She was stabilised with continuous nasogastric feeding (Similac PM 60/40, Ross Laboratories). In an attempt to wean her to bolus feeds during the daytime hours, a safflower oil based fat emulsion (Microlipid 50%, Sherwood Medical Industries) was added to her formula feeds to delay gastric emptying but without any success. Subsequently, uncooked corn starch was added to her

Department of Pediatrics,
Division of GI and
Nutrition, Louisiana
State University Medical
Center, New Orleans,
USA

Vikram Khoshoo

Departments of
Paediatrics and
Nutritional Sciences,
University of Toronto,
Division of Clinical
Nutrition

Paul B Pencharz

Division of
Gastroenterology
Ram M Reifen
Ben D Gold
Philip M Sherman

Correspondence to:
Professor Paul Pencharz,
Division of Clinical Nutrition,
The Hospital for
Sick Children,
555 University Avenue,
Toronto, Ontario,
Canada M5G 1X8.

Accepted 15 August 1991

(*Arch Dis Child* 1991;66:1447-8)