Interstitial nephritis of acute onset

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SUMMARY Interstitial nephritis was diagnosed at renal biopsy in 10 previously healthy children. All had identical clinical symptoms: anaemia, raised sedimentation rate, low glomerular filtration rate, protein and leucocytes in the urine, but no bacteria; nine also had glycosuria. Six of the children had a history of recent ingestion of drugs or a serologically proved infection, or both. One child later developed uveitis. After the acute phase all made at least partial recovery, but after a mean follow up of two years and eight months only four were without any signs of disease, three had equivocal findings, two definite renal disease, and one renal failure. Interstitial nephritis, therefore, seems to be a clinical entity often occurring without known cause or triggering factor, its prognosis is variable, and some patients may develop chronic renal failure.

Interstitial nephritis is characterised histologically by the presence of predominantly mononuclear cells in the interstitium of the kidney, tubular injury, and the absence of, or minimal, glomerular alterations. It can be subdivided into an acute form characterised by oedema and a chronic form with scarring and more widespread damage.¹ The clinical picture of interstitial nephritis of acute onset is non-specific and includes symptoms such as fatigue, fever, pallor, loss of weight, and renal failure. The main urinary findings are proteinuria, an increased number of cells, glycosuria, and often additional signs of tubular dysfunction.²⁻⁴

Although the symptoms may resemble glomerulonephritis, pyelonephritis, or acute tubular necrosis, the clinical and laboratory findings tend to be characteristic enough to lead to a diagnosis of interstitial nephritis, which can then be verified at renal biopsy. As the aetiology, the precise clinical picture, and the long term prognosis of interstitial nephritis of acute onset are undefined we report our clinical experience with 10 children, who were followed up for a mean of two years and eight months.

Patients and methods

Between 1968 and 1980 14 children with interstitial nephritis, diagnosed at renal biopsy, were seen at our hospital. This does not include children with nephronophthisis. Two of the children had rheumatoid arthritis and one familial nephritis of undefined type, and as the onset of nephritis was not acute these patients were excluded from our study. A boy

was also excluded who was a member of a previously reported family of four members suffering from severe poisoning caused by the mushroom *Cortinarius speciosissimus*.⁵ Ten children had acute onset of clinical symptoms, and examination of renal biopsy specimens showed interstitial inflammation of the kidney (interstitial infiltrate and predominantly mononuclear cells accompanied by oedema and, in most fibrosis, tubular damage, and absence of or minimal glomerular alterations). We report on the clinical picture and outcome of these 10 children. Six of the children were girls and four boys. The youngest was 6 years of age, and the others were between 10 and 15 at the onset of symptoms.

None of the children had a known pre-existing autoimmune, metabolic, or renal disease or any fluid or electrolyte disturbances before the onset of symptoms. All were admitted to hospital for investigations, including urography, renal biopsy, measurements of glomerular filtration rates (clearance of endogenous creatinine and, after 1980, of chromium labelled edetic acid), and urine analysis. Bacterial infection of the urinary tract was excluded by taking at least five cultures of urine (dipslide, Uricult), and in seven children a suprapubic aspiration of the bladder was performed. At least one sample from every child (the suprapubic aspirate if available) was cultured anaerobically and on blood or chocolate agar plates.

For each patient the antistreptolysin O titre, serological studies—for example, for staphylococcal and yersinia infections—and screening of paired serum sample, for antibodies against the herpes group and the prevalent respiratory viruses and

Table 1 Clinical course of 10 children with interstitial nephritis of acute onset

Case No	Sex	Age (years)	At onset of disease				Follow up (months)	Later	
			Duration of disease before admission (months)	Blood pressure (mmHg)	Highest serum creatinine ($\mu\text{mol/l}$)	Glomerular filtration rate (ml/min/1.73 m^2)		Glomerular filtration rate (months from onset)	Treatment and recorded abnormal findings*
1	M	6	1	115/95	101	Not done	14	Not done	No treatment, recovery
2	M	10	1.3	140/110	91	67	34	Not done	No treatment, recovery
3	F	13	0.3	115/75	134	49	52	108 (3)	Sulphonamide or nitrofurantoin for 24 months, uveitis
4	F	14	1	170/130	1126	9	24	96 (33)	Glucocorticoids for 10 months, antihypertensives
5	M	14	0.5	140/100	144	49	28	120 (9)	No treatment, sinus bradycardia
6	F	14	1.5	115/70	360	30	30	126 (32)	No treatment, recovery
7	F	15	2.5	120/80	106	50	67	108 (12), 23 (53), dialysis (67)	Sulphonamide or nitrofurantoin for 10 months, later glucocorticoids, renal transplant
8	F	15	2	125/85	405	20	14	61 (14)	Sulphonamide for one month, low serum IgA antibody
9	M	15	4	120/80	400	40	9	78 (9)	Sulphonamide for six months, proteinuria, haematuria
10	F	15	0.7	140/90	259	29	46	125 (46)	No treatment, recovery

*Deviation from normal in growth, blood pressure, serum creatinine value, urine analysis, or other sign. Conversion: SI to traditional units Creatinine: $1 \mu\text{mol/l} \approx 0.0113 \text{ mg/100 ml}$.

enteroviruses were made. In most patients anti-hyaluronidase and antideoxyribonuclease B titres were obtained in the search for streptococcal infection. Mononucleosis, salmonella, and brucella infections were excluded.

Renal biopsy specimens were examined by light microscopy, and immunofluorescence studies were performed by standard methods.

The children were followed up at the renal outpatient clinic, and measurements of glomerular filtration rates were taken as shown in Table 1.

Results

Clinical and laboratory data at presentation. All the children had previously been healthy. Their symptoms, fatigue, fever, anorexia, and gastrointestinal problems had developed within a few days. As these were non-specific renal disease was not suspected immediately, and therefore some patients were initially treated symptomatically. In some instances antibiotics were prescribed without a definite diagnosis. Details of the antibiotic treatment are given below.

On admission four children had hypertension. Erythrocyte sedimentation rate was raised in all, haemoglobin concentration was low, and both serum protein and creatinine concentrations tended to be high (Table 2). All had moderate proteinuria and pyuria ($<1 \text{ g/l}$), and nine had glycosuria. Generalised aminoaciduria was found during the acute phase in all five children in whom it was

Table 2 Laboratory findings at presentation for 10 children with interstitial nephritis of acute onset

	No of patients
Erythrocyte sedimentation rate $>50 \text{ mm/h}$	10
Haemoglobin concentration $<120 \text{ g/l}$	10
Serum:	
Creatinine concentration $>88 \mu\text{mol/l}$	9
Protein concentration $>75 \text{ g/l}$	9
IgG antibody concentration increased	8
Urine:	
Proteinuria ($>4 \text{ mg/h/m}^2$)	10
Pyuria ($>10 \text{ cells/0.9 mm}^3$)	10
Glycosuria	9
Haematuria ($>6 \text{ cells/0.9 mm}^3$)	6

Conversion: SI to traditional units—Creatinine: $1 \mu\text{mol/l} \approx 0.0113 \text{ mg/100 ml}$.

studied; and bicarbonate wasting, defined as a urinary pH greater than 6 with a serum bicarbonate concentration below 20 mmol/l , was seen in all four children in whom these data were available.

Intravenous urography showed bilaterally enlarged swollen, but otherwise normal, kidneys; kidney length was above the standard deviation calculated from the mean for body size,⁶ and in two children it exceeded two times the standard deviation above the mean. Glomerular filtration rate was low in all nine children in whom it was measured (Table 1), and serum creatinine concentration was raised in the tenth child.

By light microscopy interstitial renal inflammation was noted in all children and was accompanied by tubular damage or an increase in interstitial

fibrous tissue, or both, in eight. Immunofluorescence studies were not performed in four children and were completely negative in three others. In two children (cases 7 and 10, Table 1) intratubular material was stained by anti- β -1-C and Ig G antibody and in another child (case 6) the tubular basement membrane was stained by antifibrin and interstitial plasma cells by IgA antibody. In all children studied the glomeruli were never stained.

Possible aetiology. A thorough record of drug ingestion or poisoning was taken (Table 3). One child had been prescribed an anthelmintic drug (piperazine hydrate) 30 days before diagnosis, and he had also had a recent serologically proved streptococcal infection. Four children had been treated with antibiotics three to 16 days after onset of the symptoms, for a suspected but not proved bacterial infection of the upper respiratory tract. Two of these children received ampicillin, one penicillin, and one penicillin plus a tetanus toxoid booster. The interval between the start of the antibiotic treatment and the diagnosis of interstitial nephritis was 14 days in one of the children and 30 days in the three others. Retrospectively, it was impossible to determine whether the interstitial renal inflammation was present at the onset of the clinical symptoms or caused by or aggravated by the antibiotic treatment.

Three children had recently had a serologically proved infection (Table 3). An additional child (case 2) had a positive culture of β -haemolytic streptococcus in the throat. None of these 10 patients had positive autoimmune serology as seen by antinuclear antibody, lupus erythematosus cell phenomenon, or rheumatoid factor.

Treatment. Five children received no treatment. One child (case 4, Table 1) received methylprednisolone (4 mg/kg/day for seven days) at onset followed by oral prednisone every second day

(1 mg/kg for a week, 0.5 mg/kg for a month, with subsequent reduction of the dose during eight months). Another child (case 7, Table 1) received chemotherapy first and as the symptoms worsened during the next two years received prednisone (0.75 mg/kg every second day for one month then 10–20 mg every second day). The three other children (cases 3, 8, and 9) were given chemotherapeutic agents (sulphafurazol 0.1 g/kg/day or nitrofurantoin 3 mg/kg/day) for half to two years even though their urine analysis did not show any bacterial growth.

Clinical and laboratory outcome. All children except one (case 7, Table 1) became free of symptoms during a follow up period of nine to 67 months (mean two years and eight months), and in most the laboratory values returned to normal. At the end of follow up the serum creatinine concentrations of nine of the 10 children were normal. Glomerular filtration rate was within normal limits in five; moderately decreased (>60 ml/min/1.73 m²) in two; and steadily declined to end stage renal failure in only one (case 7). In two children (cases 1 and 2) glomerular filtration rate was not measured at the end of follow up; their physical examination, serum creatinine concentration, erythrocyte sedimentation rate, haemoglobin concentration, and urine were normal.

Four of the 10 children made a complete recovery; all symptoms of renal disease resolved and growth, development, blood pressure, urine analysis, and serum creatinine concentration were normal. One child (case 5) had normal urine and glomerular filtration rate but had sinus bradycardia, one (case 3) had chronic uveitis without signs of renal disease, one (case 9) proteinuria (<1 g/day) and microscopic haematuria, one (case 8) reduced glomerular filtration rate, and one (case 4) normal urine and glomerular filtration rate but arterial hypertension. The tenth child (case 7), a 15 year old girl, developed hypertension and end stage renal failure. Subsequently, she was given haemodialysis and later received successfully a renal transplant.

Discussion

Interstitial nephritis of acute onset is a rare renal disorder in childhood. The symptoms are non-specific, and it can be diagnosed readily only when the disease is sufficiently severe to warrant a renal biopsy. Mild or subclinical episodes probably remain undiagnosed, and the true number of occurrences is difficult to estimate.

The clinical picture of our patients was uniform with low grade fever, anaemia, and increased

Table 3 Possible aetiology in 10 children with interstitial nephritis of acute onset

Aetiological factors	No of patients (case no)
Drugs within one month before onset of symptoms (piperazine hydrate)	1 (1)
Drugs after presentation of symptoms (penicillins)	4 (2, 4, 7, and 8)
Signs of recent infection*:	
Streptococcus	1 (1)
<i>Yersinia enterocolitica</i>	1 (4)
Combined influenza virus, adenovirus, and rotavirus	1 (5)

* $\geq$ Twofold increase in antibody titre.

erythrocyte sedimentation rate and serum creatinine and protein concentrations. Leucocytes and glucose, but no bacteria, were present in the urine. Possible causative or associated factors did not influence the symptoms in any way; the clinical manifestations were identical after recent streptococcal, yersinia, or viral infections or after ingestion of drugs, any of which could have been aetiological factors. The uniformity of the clinical presentation in our study and its similarity to earlier reports²⁻⁴ suggest that interstitial nephritis of acute onset is a clinical syndrome caused by a variety of factors.

In certain subjects a genetically determined immunological reactivity may be the primary determinant, and a variety of stimuli may trigger an inflammatory reaction within the parenchyma of the kidney in such subjects. The fact that uveitis is such a common associated manifestation,⁷ although we found it in only one patient, further supports the idea of a primary immunological deviation of patients with interstitial nephritis of acute onset.

Ellis *et al* found a recent streptococcal infection to be the causative factor in most of their patients.³ We could not, however, confirm this in our study; only one child had a raised antistreptolysin O titre, indicating a recent streptococcal infection, and extensive investigation excluded this as an aetiological factor in the other children.

Different modes of treatment have included symptomatic treatment, chemotherapy, and treatment with glucocorticoids.^{3 4 8} Our patients with the least severe symptoms received no treatment, and our most severely affected patient was given glucocorticoids, which relieved her clinical symptoms but had no effect on renal state, although other reports have claimed a favourable effect on renal function.^{3 4 8}

The prognosis of interstitial nephritis in childhood is often considered to be favourable. All the patients reported by Ellis *et al*³ and Burghard⁴ were without clinical symptoms after a follow up of 1.5–10 years and had normal renal function. In contrast, only

four of our 10 patients could be considered to have made a total recovery after a mean follow up time of two years and eight months when strict criteria were applied. This indicates that in certain subjects nephritis may be a severe disease and even progress to end stage renal failure.

In conclusion interstitial nephritis is a rare syndrome in childhood, but paediatricians should be aware of it and suspect it clinically if signs of tubular dysfunction are present. Diagnosis may then be verified at renal biopsy. Although most patients recover completely, some may have a prolonged disease, and a few may develop chronic renal failure.

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