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BRIEF REPORT

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Tubulointerstitial nephritis and uveitis in monozygotic twin boys

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Abstract We describe monozygotic male twins who developed tubulointerstitial nephritis and uveitis (TINU) almost 2 years apart. They presented with non-specific symptoms and were noted to have glycosuria and renal impairment. Both children have uveitis. One had biopsy-proven interstitial nephritis and the other had biochemical evidence of transient tubular dysfunction. While the renal parameters improved, they are still under treatment for uveitis. The occurrence of TINU in identical twins at an interval of just under 2 years supports a strong genetic element in the aetiology of this syndrome. We believe this is the first report of male twins with TINU.

Keywords Tubulointerstitial nephritis and uveitis · Male twins · Kidney biopsy

Introduction

Tubulointerstitial nephritis with uveitis (TINU) is an uncommon syndrome. Since its description in 1975 [1], less than one hundred cases have been reported. We describe TINU in male twins. The unusual feature was the presentation 2 years apart.

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Case reports

Case 1, June 2000

The first twin presented at 8 years of age with nocturnal enuresis and polydipsia. Urine dipstick testing revealed glucose, but his blood sugar and a glucose tolerance test were normal. He was therefore referred to the nephrology service.

He had not had significant medical problems in the past. There was no history of ingestion of any medications or drugs, except for amoxicillin for an upper respiratory infection. His height was 136 cm (75th percentile) and his weight was 26 kg (50th percentile). Physical examination was unremarkable. Examination of the eyes with a hand-held ophthalmoscope was normal. His investigations are outlined in Table 1. Plasma phosphate (1.38 mmol/l), albumin, and other electrolytes were normal. There was a mild generalised aminoaciduria (elevated levels of aspartic acid, threonine, serine, asparagine, glutamine, glycine, alanine, cystine, valine, citrulline, tyrosine, lysine, histidine), and glucosuria in the presence of a normal plasma glucose. An autoantibody screen (antinuclear antibodies and smooth muscle, liver/kidney microsomal and keratin antibodies) was negative. Complement components C3 and C4 were normal. Serology for hepatitis viruses, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and mycoplasma was negative. A renal ultrasound scan was normal. A renal biopsy was planned but not performed because renal function improved without medical intervention. He was diagnosed as having a mild interstitial nephritis of unknown cause.

An ophthalmic review 2 years later, at the time of his brother's presentation revealed anterior uveitis. His investigations are outlined in Table 1. An autoantibody screen was negative. The uveitis initially responded well to topical steroid therapy, but subsequently relapsed. At the time of ophthalmological relapse he appeared well. The plasma creatinine continued to be normal (49 μmol/l) and the urine remained negative for protein, glucose, and aminoaciduria. Urinary β_2-microglobulin was 0.19 mg/l (normal <0.3 mg/l). He is receiving ongoing treatment with topical steroids.

Case 2, March 2002

The second twin presented 21 months after his brother at the age of 10 years with nocturnal enuresis associated with generalised malaise and myalgia. Urine dipstick testing revealed glucose with a normal blood sugar and a normal glucose tolerance test, following which he was referred to us.

While he had a history of peanut and egg allergy and mild asthma, there was no other significant medical history. There was no history of ingestion of any medications or drugs. His height was 145 cm (75th percentile) and his weight was 35 kg (75th percen-

Table 1 Investigations for twin 1

Test	Presentation	6-month follow-up	2-year follow-up
Urine			
Dipstix	1+ protein 1+ glucose	Negative	Negative
Protein/creatinine ratio (normal <23 mg/mmol)	9	9	4
β_2-Microglobulin (normal <0.3 mg/l)	Not done	0.7	0.19
Amino acid	Generalised aminoaciduria	Normal	Normal
Glucose	1/2%	Negative	Negative
Plasma creatinine (μmol/l)	107	64	58
Antinuclear antibodies	Negative	Negative	Negative

Table 2 Investigations for twin 2

Test	Presentation	6-month follow-up	1-year follow-up
Urine			
Dipstix	2+ protein 1+ glucose	Negative	Negative
Protein/creatinine ratio (normal <23 mg/mmol)	154	9	9
β_2-microglobulin (normal <0.3 mg/l)	1.5	1.8	0.04
Amino acid	Generalised aminoaciduria	Normal	Normal
Glucose	1/4%	Negative	Negative
Plasma creatinine (μmol/l)	107	58	49
Antinuclear antibodies	Negative	Negative	Negative

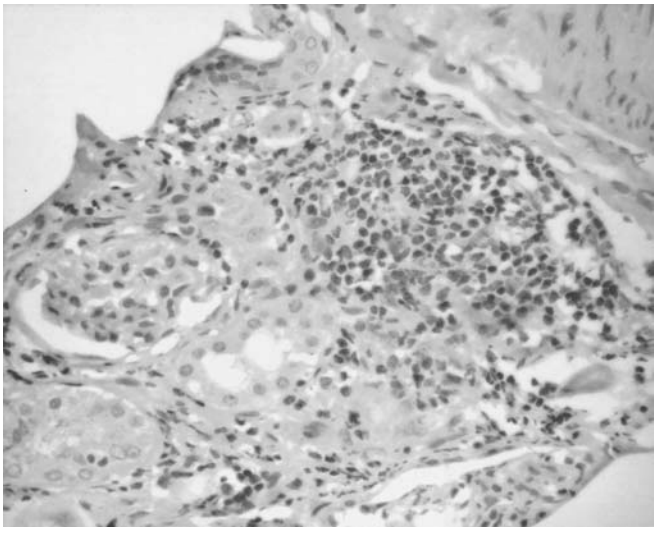

Fig. 1 Medium-power view of the interstitial infiltrate (note normal glomerulus)

tile). Physical examination was unremarkable. His investigations are outlined in Table 2. He had mild generalised aminoaciduria with elevated levels of the same amino acids in the urine as his brother. The C-reactive protein level was 40 mg/l (normal 0–6 mg/l). The plasma phosphate (0.82 mmol/l), albumin, and other electrolytes were normal as were complement components C3 and C4. An autoantibody screen was negative and there was no serological evidence of infection with mycoplasma, hepatitis viruses, EBV, or CMV.

An ophthalmic review showed bilateral anterior uveitis; 6 weeks after onset of clinical symptoms, a renal biopsy revealed an abnormal tubulointerstitial compartment with widespread separation of tubules by an interstitial infiltrate, consisting of chronic inflammatory cells (including plasma cells), and large numbers of eosinophils. There was granularity and vacuolation of the tubular epithelial cell cytoplasm and a patchy tubulitis. (Fig. 1) The biopsy findings were consistent with those previously described in interstitial nephritis with uveitis. He was treated with oral and topical corticosteroids. Follow-up investigations are shown in Table 2. As expected, both had the same HLA type, which was HLA-A2, B18, 51, CW0701, 14, BRB10101/02/04,14.

Discussion

Both twins presented with similar non-specific symptoms. In both twins, the presence of an elevated plasma creatinine, aminoaciduria, and glycosuria indicated tubular dysfunction. A kidney biopsy confirmed tubulointerstitial nephritis in twin 2. The presence of uveitis confirmed the diagnosis of TINU. His brother had similar biochemical evidence of renal tubular dysfunction that recovered completely. This suggested tubulointerstitial nephritis. Anterior uveitis on ophthalmic review indicated the likelihood of TINU. A renal biopsy was not considered in the first twin, as the renal function had become normal.

Serology of both twins excluded infection with mycoplasma, EBV, CMV, and hepatitis B and C. The autoantibody screen and complement concentrations were normal, excluding systemic illnesses such as systemic lupus erythematosus. While the first twin had taken a course of amoxicillin, his brother had not taken any medications that may have triggered tubulointerstitial nephritis.

TINU was first described in 1975. There is a female predominance of 3:1 [2]. Acute tubulointerstitial nephritis has been associated with infectious agents [3], toxins, drugs [4], and systemic disease, but there is little known about the pathogenesis associating tubulointerstitial nephritis with eye manifestations. A recent report has provided evidence of transient immune dysregulation during active TINU [5] and suggested an abnormal response to infection.

There has been one previous report of monozygotic female twins with acute interstitial nephritis, one of whom had bilateral anterior uveitis [6]. Their HLA type was A24,28; BW 22,40; CW3; DR4,W6. The twins described in our report do not share any HLA alleles with the previously described twins. As not all patients with TINU mentioned in previous case reports have had HLA typing performed, it is difficult to comment on whether any particular HLA alleles predispose to TINU. However, it is interesting that the twins mentioned in our report share HLA-A2 with a previously reported case in 1995 [7]. However, they do not show HLA-CW3, HLA-A24, or HLA-DR6, which have all been previously described as common alleles in patients with TINU [8, 9]. A recent report [10] suggested a strong association with HLA-DRB1*0102 and that the alpha-beta dimer encoded by HLA-DQA1*01/DQB1*05 may confer risk for development of this disease.

It is not possible to explain the aetiology of TINU completely, but the presence of this rare syndrome in monozygotic twins adds weight to a crucial genetic susceptibility to the pathogenesis of TINU. The reasons for a female preponderance in TINU (3:1) are unclear. Thus it is less common in males and it is unusual that our patients are male twins, while the previous set of twins described was female [6]. The other report describing siblings with tubulointerstitial nephritis, one of them showing uveitis, was again of sisters [11]. Also, the occurrence of the syndrome 2 years apart is strong evidence of genetic predisposition.

In both cases there was complete recovery of renal function. It is interesting to note the presence of persistently elevated β_2-microglobulin levels in both twins at 6 months after the episodes, indicative of ongoing renal tubular dysfunction after normalisation of other indicators of proximal tubular function. The urinary β_2-microglobulin levels did normalise later. Urinary examination in the acute phase did not reveal eosinophils, but eosinophils are not seen in all cases of tubulointerstitial nephritis. Both twins are receiving ongoing treatment for chronic eye manifestations, and it is well known that the eye problems tend to be chronic and relapsing in TINU [2].

The presence of tubulointerstitial nephritis should alert the physician to the possibility of uveitis, which might be asymptomatic, as in the case of the twins described, and a prompt diagnosis could help in the early management of uveitis. While the renal prognosis is generally considered favourable, certain reports [2] suggest that some patients may need renal replacement therapy. The long-term outcome has also been linked to the degree and duration of infiltration by inflammatory cells [12].

In conclusion, it is important to be aware of TINU to be able to achieve a prompt diagnosis in children with renal impairment and tubular dysfunction with minor symptoms so that appropriate management can be started early. The aetiology remains unknown, but these patients suggest a strong genetic influence.

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