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Etiologies of asymptomatic microscopic hematuria in children – systematic review of 1092 subjects

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Abstract

Background: Asymptomatic microscopic hematuria is common in children. No systematic review providing an evidence based approach for the differential diagnosis of these children has been performed.

Contents: Multiple data bases were search. The PRISMA criteria were followed. Data regarding the etiology of the hematuria were extracted using a standardized extraction tool. Seven studies encompassing 1092 children (857 with isolated microscopic hematuria and 235 with combined microscopic hematuria and proteinuria), comprise this review. A total 42.4% of isolated microscopic and 81.3% of microscopic hematuria and proteinuria subjects had identified etiologies. Thin basement membrane nephritis (15.2%), IgA nephropathy (10.4%), and hypercalciuria without nephrolithiasis (7.7%), were the most common etiologies among children with isolated microscopic hematuria. IgA nephropathy (44.3%), thin basement membrane disease (12.8%), and mesangial proliferative glomerulosclerosis (8.9%) were the most common etiologies among children with combined microscopic hematuria and proteinuria.

Conclusion: The present study provides an evidenced based resource, based on a systematic review, for the differential diagnosis of asymptomatic hematuria in children. Additionally, these observations suggest that children with isolated microscopic hematuria should be followed for persistence of hematuria or the development of proteinuria. Children with combined microscopic hematuria and proteinuria should be comprehensively evaluated.

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Keywords: children; diagnosis; etiology; hematuria; proteinuria.

Introduction

Asymptomatic, microscopic hematuria is a common problem in children. The prevalence rate of microscopic hematuria in two or more samples of urine in school-aged children has been estimated at 1%–2% [1, 2]. The potential etiologies of microscopic hematuria in children are myriad but mostly benign [3]. Nevertheless, chronic nephritis progressing to renal failure occurs in childhood, is often asymptomatic in its early stages, and may present with isolated hematuria with or without accompanying proteinuria [4]. Urinalysis is often used to screen for these disorders. While numerous case series and editorials appear in the literature a systematic review of isolated hematuria has not been reported. The purpose of this systematic review was to (1) determine the specific etiologies of asymptomatic microscopic hematuria with and without proteinuria; (2) determine the relative prevalence of etiologies across a wide spectrum of patients and; (3) provide evidence to guide the diagnostic evaluation of these patients.

Methods

Protocol

This study followed the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRSIMA) guidelines [5].

Eligibility

The inclusion criteria for this review were: (1) Subjects aged 18 years or under with asymptomatic microscopic hematuria±proteinuria identified on at least two occasions and; (2) experimental, observational, or cross-sectional studies of 10 or more patients. Case reports,

editorials, and review articles were excluded. Patients with gross hematuria, history of known illness associated with microscopic hematuria, active symptoms of any illness, or family history of glomerular disease were excluded.

Information sources

EMBASE and PubMed were searched electronically. The bibliographies of all of the selected studies were reviewed manually. After contact with one study author, the bibliography of an additional paper that had been unpublished during the time of the original search was reviewed.

Search

The main search terms were "hematuria", case series, and cohort; the following filters were used: human, age infant (birth–23 months), age preschool (2–5 years), age child (6–12 years), and age adolescent (13–18 years). Four consecutive searches were run using each individual age filter; duplicates were eliminated during screening. A second search used the following search terms: "hematuria", "children", and "etiology", along with the filter "humans". The results of all searches were pooled for screening by the authors. Studies that did not provide abstracts or were in foreign languages without English abstracts were excluded.

Study selection

Each article was independently evaluated by two authors. In cases where the study populations overlapped due to nationwide screening, the study that most closely met inclusion criteria was selected. Differences in judgment were resolved first by consensus; ties were adjudicated by the third author.

Data collection

For each selected study, the following information was recorded: inclusion criteria, exclusion criteria, number of patients, age range, diagnostic criteria, specific etiologies of microscopic hematuria, and country of origin. The etiologies of microscopic hematuria, were assigned to one of two groups: isolated microscopic hematuria and combined microscopic hematuria and proteinuria. Data extraction was performed by one author (MMC) and then reviewed by another (MTD). The major categories of disease included hereditary and non-hereditary glomerulonephritides, immune vasculitides, thin basement membrane disease, lupus erythematosus, Alport syndrome, hypercalciuria with or without nephrolithiasis, and anatomical abnormalities. Within each category, specific etiologies were catalogued from those studies that provided specific data.

Sources of bias across studies

As the etiologies identified in the majority of studies included in this review were based mainly on the results of renal biopsy, non-glomerular causes of microscopic hematuria may be underrepresented. Discrepancies within individual studies between data described in the text and data displayed in tables were another potential source of error. Differences in exclusion criteria among the selected studies and inconsistencies in nomenclature posed additional risks for bias.

Ethics

This study did not involve any direct contact with primary patient source documents but used public data sources precluding the need for IRB approval or patient consent.

Results and discussion

Study selection

The results of the literature search are shown in Figure 1. Searches of the EMBASE and PubMed databases provided a total of 3607 citations. An additional 11 citations were found by extensively searching the bibliographies of selected articles as well as the bibliography of one additional article provided after contact with a study author. From the 3618 studies identified, 3480 studies were excluded after a cursory review of the title and abstract with 138 remaining. The full texts of the remaining 138 articles were reviewed in detail. One hundred and thirty-one were excluded: 124 failed to provide specific disease information or did not meet inclusion criteria; six reports had overlapping populations with other studies; and one report included data from adult subjects that could not be separated from pediatric subjects.

Study characteristics and outcomes

The characteristics of the seven studies that met the inclusion criteria and comprise the basis of this review are shown in Table 1 [2, 4, 6–10]. Piqueras et al. included only patients in whom non-glomerular causes were found [8]. Trachtman et al. excluded from biopsy patients in whom the following were found: proteinuria, GFR below 80 mL/min/1.73 m^2, a blood pressure above 95th percentile, serum C3 level below 50 mg/dL, or anatomic abnormality of the urinary tract [10].

The reports ranged in size from 26 to 452 participants per study. Together, these reports represent a worldwide sample (Iran, Finland, Japan, Korea, the UK, and the USA). Three studies summarized population-based screenings in Finland [2], Japan [9], and Korea [2, 4]; two reports [6, 7]

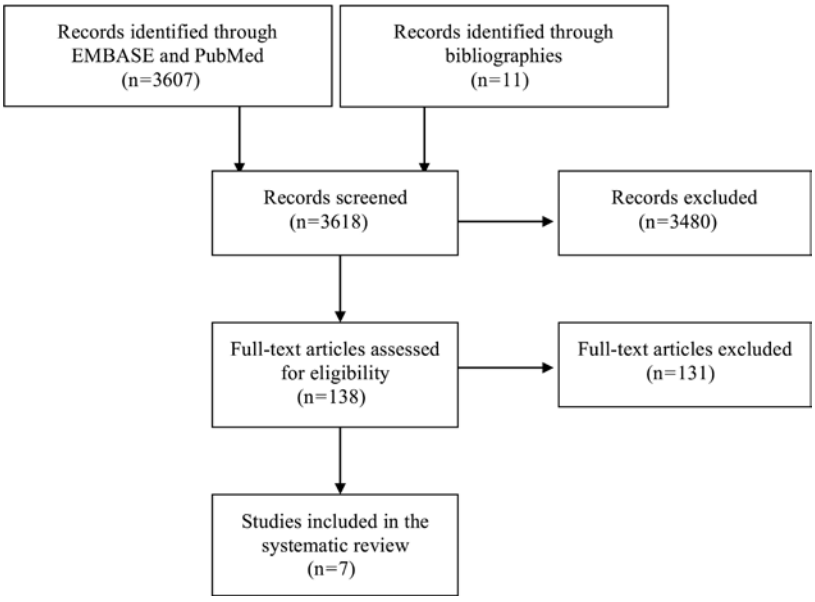

Figure 1: Results of the literature search.

Table 1: Summary of research articles.

Article	Isolated hematuria (IH)	Combined hematuria-proteinuria (CHP)	Ages (M:F)	Country of origin
Moghtaderi et al. [6]	26	N/A	6–14 years (unknown M:F)	Iran
Lee et al. [4]	289	163	11±2.7 years (1.2:1)	Korea
Bergstein et al. [7]	342	N/A	1 month–18 years (1:1.1)	USA
Piqueras et al. [8]	131	N/A	10.1±3.7 years (unknown M:F)	UK
Hisano and Ueda [9]	N/A	66	6–15 years (1.5:1)	Japan
Trachtman et al. [10]	42	N/A	3–19 years (unknown M:F)	USA
Vehaskari et al. [2]	27	6	8–17 years (1:1.5)	Finland

were prospective studies performed at single centers and two studies [8, 10] were retrospective studies from single centers. The total number of patients included in this review is 1092.

The underlying conditions by study associated with isolated, asymptomatic, microscopic hematuria (IH) in children are shown in Table 2. All but two studies included in this review represent data based on renal biopsies. All diagnoses reported by Moghtaderi et al. [6] and all but two diagnoses reported by Bergstein et al. [7] were identified by non-invasive methods including laboratory and serology studies, intravenous pyelography (IVP), ultrasonography, and cystography. The results of those investigations are reported in Table 2. The two patients reported by Bergstein et al. who did undergo biopsy were found to have IgA nephropathy and membranoproliferative glomerulonephritis [7]. Moghtaderi et al. also identified one patient with oncocystoma after a surgical procedure performed following ultrasonography [6]. Vehaskari et al. reported a patient with uretopelvic stenosis identified by IVP [2]. Of 131 patients who underwent renal biopsy, four had normal biopsy results but were discovered to have hypercalciuria after further investigation (one with and three without nephrolithiasis) [8]. The underlying conditions associated with combined asymptomatic microscopic hematuria and proteinuria (CHP), by study, are shown in Table 3. In the study by Hisano et al., 20 patients were excluded from renal biopsy based on the results of non-invasive clinical investigations [9]; 10 patients with Henoch-Schönlein purpura were identified by history of purpura and joint pain; one patient with Alport's syndrome hearing loss and a remarkable family history and; one patient with lupus nephritis had a history of butterfly rash and arthralgia. These patients are included in Table 3. Moghtaderi et al. [6], Bergstein et al. [7], Piqueras et al. [8], and Trachtman et al. [10] did not report any patients with CHP.

Table 2: Etiologies for isolated microscopic hematuria (IH).

	Moghtaderi et al. [6]	Lee et al. [4]	Bergstein et al. [7]	Piqueras et al. [8]	Trachtman et al. [10]	Vehaskari et al. [2]
No diagnosis/normal	5	136	274	32	25	22
IgAN		46	1	39	1	2
TBMN		97		23	10	
MGN		2				
PSGN		4	4			
Alport syndrome		1		2	1	
MPGN			1			
MesPGN		1				
Lupus		1				
Oligomeganephronia		1				
Other GN[a]				16		1
Relative uretopelvic stenosis						2
Double calyceal collecting system (IVP)			2			
Hypercalciuria without nephrolithiasis	7		56	3		
Hypercalciuria with nephrolithiasis			1	1		
Nephrolithiasis	13					
Oncocystoma	1					
Solitary kidney			1			
Unilateral hypoplasia			1			
Vesicoureteral reflux (grade 3)			1			
Hilar vasculopathy/vascular C3				15	5	

[a]Other GN refers to focal proliferative glomerulonephritis, hereditary nephritis, and immune complex glomerulonephritis. IgAN, Immunoglobulin A nephropathy; TBMN, thin basement membrane disease; PSGN, poststreptococcal glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; MesPGN, mesangial proliferative glomerulonephritis; GN, glomerulonephritis; HSPN, Henoch-Schönlein purpura nephritis; MGN, membranous glomerulonephritis; GN, glomerulonephritis.

Table 3: Etiologies for combined microscopic hematuria and proteinuria (CHP).

	Lee et al. [4]	Hisano and Ueda [9]	Vehaskari et al. [2]
No Diagnosis	40	0	4
IgAN	75	29	
MesPGN	5	16	
TBMN	30		
PSGN	4		
HSPN		10	
MGN		4	
Alport syndrome	3	1	
MPGN	2	3	
FSGS	3	2	1
Lupus		1	
MCNS	1		
Polyarteritis			1

IgAN, Immunoglobulin A nephropathy; MesPGN, mesangial proliferative glomerulonephritis; TBMN, thin basement membrane disease; PSGN, post-streptococcal glomerulonephritis; HSPN, Henoch-Schönlein purpura nephritis; MGN, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome.

Synthesis of results and summary of evidence

The underlying disease processes associated with asymptomatic microscopic hematuria, both isolated (IH) and combined with proteinuria (CHP) are shown in Table 4.

The majority of children with IH had no identifiable underlying pathology (57.6%). Thin basement membrane disease was the most commonly identified cause of isolated microscopic hematuria (15.2%), followed by IgA nephropathy (10.4%), hypercalciuria without nephrolithiasis (7.7%), and hilar vasculopathy (2.3%). Other glomerulonephritides, including focal proliferative, hereditary, and immune complex glomerulonephritis, were associated with IH in 2% of patients. Nephrolithiasis was found in 1.5% of patients. Other causes of IH accounted for <1% of patients with IH.

The majority of children with CHP had an identified etiology for these findings (81.3%). IgA nephropathy was the most commonly identified etiology (44.3%), followed by thin basement membrane disease (12.8%), mesangial

Table 4: Summary of etiologies for IH and CHP.

	IH	CHP
No diagnosis/normal	494 (57.6%)	44 (18.7%)
IgAN	89 (10.4%)	104 (44.3%)
TBMN	130 (15.2%)	30 (12.8%)
MGN	2 (0.23%)	4 (1.7%)
PSGN	8 (0.93%)	4 (1.7%)
HSPN	0	10 (4.3%)
FSGS	0	6 (2.6%)
MCNS	0	1 (0.43%)
Alport syndrome	4 (0.47%)	4 (1.7%)
MPGN	1 (0.12%)	5 (2.1%)
MesPGN	1 (0.12%)	21 (8.9%)
Lupus	1 (0.12%)	1 (0.43%)
Oligomeganephronia	1 (0.12%)	0
Polyarteritis	0	1 (0.43%)
Other GN[a]	17 (2.0%)	0
Relative uretopelvic stenosis	2 (0.23%)	0
Double calyceal collecting system (IVP)	2 (0.23%)	0
Hypercalciuria without nephrolithiasis	66 (7.7%)	0
Hypercalciuria with nephrolithiasis	2 (0.23%)	0
Nephrolithiasis	13 (1.5%)	0
Oncocystoma	1 (0.12%)	0
Solitary kidney	1 (0.12%)	0
Unilateral hypoplasia	1 (0.12%)	0
Vesicoureteral reflux (grade 3)	1 (0.12%)	0
Hilar vasculopathy/ vascular C3	20 (2.3%)	0
Total	857	235

[a]Other GN refers to focal proliferative glomerulonephritis, hereditary nephritis, and immune complex glomerulonephritis. IH, Isolated microscopic hematuria; CHP, combined microscopic hematuria and proteinuria; IgAN, Immunoglobulin A nephropathy; TBMN, thin basement membrane disease; PSGN, poststreptococcal glomerulonephritis; HSPN, Henoch-Schönlein purpura nephritis; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis; MesPGN, mesangial proliferative glomerulonephritis; MGN, membranous glomerulonephritis; GN, glomerulonephritis.

proliferative glomerulonephritis (8.9%), Henoch-Schönlein purpura nephritis (4.3%), focal segmental glomerulosclerosis (2.6%), and membranoproliferative glomerulosclerosis (2.1%). Membranous glomerulonephritis, post-streptococcal glomerulonephritis, and Alport's syndrome were each seen in 1.7% of patients. Minimal change nephrotic syndrome, lupus nephritis, and polyarteritis occurred in <1% of patients.

Risk of bias

The studies included in this review ranged in size from 26 to 452 subjects; the largest study [4] accounted for 41.4% of the total sample and may have introduced sampling error into the data synthesis. In contrast, patients originated from six different countries and multiple continents. Three studies were population-based [2, 4, 9] and the remaining four studies represented individual clinical sites [6–8, 10].

The etiologies reported in five of the studies [2, 4, 8–10] were based primarily on biopsy specimens. These studies accounted for 66% of patients included in this review (57% with IH, 100% with CHP). As a result, non-glomerular causes of microscopic hematuria in both IH and CHP may be underrepresented in the data synthesis.

Inconsistencies in the nomenclature of glomerulonephropathies as well as the diagnostic evaluation and definitions of specific glomerular findings are the result of broad time range of the studies included in this review (1979–2014). Patients diagnosed with hilar vasculopathy and/or vascular C3 deposition were grouped together as were patients with miscellaneous glomerulonephritis, which includes focal proliferative glomerulonephritis, hereditary nephritis, and immune complex glomerulonephritis.

Hypercalciuria may be underrepresented as a cause of IH in this review since only three of seven studies screened for it. Historically, microscopic hematuria is often attributed to hypercalciuria. , In the data presented in this review, hypercalciuria without nephrolithiasis was found in only 7.7% of patients with IH; hypercalciuria and nephrolithiasis was rare in this review (0.23%). Feld et al. found hypercalciuria as the etiology of IH in only 11% of patients [11]. Stark et al. found hypercalciuria to be a rare cause of microscopic hematuria (2.5% of patients), but more common in children presenting with gross hematuria [12].

Differences in exclusion criteria may have introduced bias when the studies were combined. Trachtman et al. excluded from biopsy patients in whom the following were found: proteinuria, GFR below 80 mL/min/1.73 m^2, a blood pressure above 95th percentile, serum C3 level below 50 mg/dL, or anatomic abnormality of the urinary tract [10]. The other studies that reported data on biopsy specimens included all patients with persistent IH or any CHP. Finally, differences in the timing of studies (retrospective versus prospective), discrepancies in reporting within and between studies, and variability in patient evaluation may all have contributed to systematic bias in this review.

Conclusions

Isolated hematuria with or without accompanying proteinuria is a common problem in pediatrics. Synthesis of data from seven studies encompassing 1092 children demonstrates that more than 40% of patients with IH and more than 80% of patients with CHP have underlying pathology. The type and relative prevalence of these disorders provides guidance for the thoughtful evaluation of the child with isolated hematuria. While a limited evaluation may be prudent for the child with IH a comprehensive history and laboratory investigation, may be necessary for the child with CHP. In either case long-term follow-up is recommended for all patients given the substantial risk of underlying disease. As with any systematic review, potential sources for bias exist.

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