Papers

New renal scarring in children who at age 3 and 4 years had had normal scans with dimercaptosuccinic acid: follow up study

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Abstract

Objective: To determine up to what age children remain at risk of developing a new renal scar from a urinary tract infection.

Design: Follow up study. Families of children who had normal ultrasound scans and scanning with dimercaptosuccinic acid (DMSA) after referral with a urinary tract infection when aged 3 (209) or 4 (220) were invited to bring the children for repeat scans 2-11 years later. A history of infections since the original scan was obtained for children not having a repeat scan.

Setting: Teaching hospital.

Subjects: Children from three health districts in whom a normal scan had been obtained at age 3-4 years in 1985-1992 because of a urinary tract infection.

Main outcome measure: Frequency of new renal scars in each age group.

Results: In each group, about 97% of children either had repeat scanning (over 80%) or were confidently believed by their general practitioner or parent not to have had another urinary infection. The rate of further infections since the original scan was similar in the 3 and 4 year old groups (48/176 (27%) and 55/179 (31%)). Few children in either group known to have had further urinary infections did not have repeat scanning (3/209 (1.4%) and 4/220 (1.8%)). In the 3 year old group, 2.4% (5/209) had one or more new kidney scars at repeat scanning (one sided 95% confidence interval up to 5.0%), whereas none of the 4 year olds did (one sided 95% confidence interval up to 1.4%). The children who developed scars were all aged under 3.4 years when scanned originally.

Conclusions: Children with a urinary tract infection but unscarred kidneys after the third birthday have about a 1 in 40 risk of developing a scar subsequently, but after the fourth birthday the risk is either very low or zero. Thus the need for urinary surveillance is much reduced in a large number of children.

Introduction

Agreement is widespread that renal scars may be caused by a urinary tract infection in the presence of vesicoureteric reflux, and that this is most likely to occur in very young children.[1] This concept underpins most guidelines for investigating children after urinary infections, including the consensus document from a multidisciplinary working group of the Royal College of Physicians.[2] However, the age beyond which there is no further risk of developing a first scar is uncertain, and this uncertainty was reflected by dissent in the working group about age adjusting imaging schedules.[2]

Evidence that new scars might develop after the age of 4 years, even up to the age of 10,[3-9] is all based on intravenous urography, which is now known to be insensitive in young children; new scars sometimes take years to become clearly evident, whereas isotope scanning with dimercaptosuccinic acid (DMSA) detects them immediately.[10-12] Some of these apparently new scars might therefore have been from earlier urinary infections, and the age after which little or no risk exists of acquiring a new scar may be much younger than 10 years. In two serial studies using DMSA scanning,[13 14] the only child who developed new scarring was aged 8 months at the time of her normal first scan (I G Verber, personal communication).

Because this evidence suggested that older children with normal kidneys had little risk of developing a scar, we adopted a policy from 1985 (widely used throughout the former Northern health region) whereby children with normal ultrasonography and normal DMSA scan after the fourth birthday had no follow up. Younger children with normal scans are monitored, and have repeat scanning and micturating cystography if they have a further infection before their fourth birthday. One child with a normal scan at 3.4 years followed by further urinary infections had extensive scarring when scanned again four years later. Therefore, to assess the safety of our protocol we invited families whose children had had normal scans when aged 3 or 4 years to bring their children back for repeat scanning two to 11 years later.

Patients and methods

We identified two groups of children from those in the Northumberland, Newcastle, and North Tyneside health districts who had been referred between January 1985 and December 1992 with a urinary tract infection and who had normal ultrasonography and a normal DMSA scan: (*a*) 3 year olds (aged 3.00-3.99

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years) (n = 209) and (*b*) 4 year olds (aged 4.00-4.99 years) (n = 220). We invited the families to bring their child for scanning because of the very small risk that the child may have developed a scar from a subsequent urinary infection, and the children's general practitioners were informed. We asked the parents of all the children to estimate how many urinary infections had occurred since the original scan. The study had approval from the joint ethics committee of Newcastle University and Newcastle Health Authority, and we obtained informed consent from the parent and child.

For children who returned for DMSA scanning, a urine sample was checked by phase contrast microscopy,[15] and scanning was performed as part of the medical physics department's routine clinical service; the images were acquired two hours after intravenous technetium-99m-DMSA at a dose scaled between 2 MBq/kg in infants and 1 MBq/kg in older children and were reported among the routine scans by a single experienced observer. The computer image was evaluated for scarring directly from the screen, and the apparent distribution of radioactivity between the two kidneys was noted. Children with a urinary infection on the day that they were due to be scanned had it postponed for 3 months while they received antibiotics; all had sterile urine subsequently. Children in whom scanning showed renal scars had confirmatory investigations—combinations of ultrasonography, micturating cystography, and urography.

Families who had not responded to their first letter of invitation were sent a second letter, and the general practitioner was contacted for a record of the child's urinary infections; the general practitioners often contacted the families through the health visitor to ensure that they clearly understood the issues. Families who had moved were traced through the family health services authority; those still living in the United Kingdom were offered repeat scanning in Newcastle or in another region.

Table 1 Attendance of children for repeat scanning and details of urinary infections in non-attenders. Values are numbers (percentages) of children

Attendance	3 year olds (n=209)	4 year olds (n=220)
Scanned or had no more infections:		
Scanned	176 (84)	179 (81)
Not scanned, parent and GP confirmed no infections	23 (11)	15 (7)
Not scanned, GP alone confirmed no infections	4 (2)	19 (9)
Died, and kidneys normal at postmortem	1 (0)	0
Total	204 (98)	213 (97)
Not scanned, despite having more infections:		
Not scanned, though parent and GP confirmed infections	1 (0)	2 (1)
Not scanned, though GP confirmed infections	2 (1)	2 (1)
Total	3 (1)	4 (2)
Not traced:		
Moved abroad	2 (1)	2 (1)
Travelling family	0	1 (0)
Total	2 (1)	3 (1)

GP=general practitioner.

Table 2 Mobility of families between original scanning and repeat scanning. Values are numbers (percentages) of children

	3 year olds		4 year olds	
	Invited (n=209)	Scanned (n=176)	Invited (n=220)	Scanned (n=179)
Did not move	127 (61)	110/127 (87)	144 (65)	123/144 (85)
Moved within health region	63 (30)	51/63 (81)	63 (29)	54/63 (86)
Moved to another health region*	17 (8)	15/17 (88)	7 (3)	2/7 (29)
Moved abroad, but contacted	0		3 (1)	0/3
Moved abroad, not traced	2 (1)	0/2	2 (1)	0/2
Unknown whereabouts	0		1 (0)	0/1

*Four 3 year olds and two 4 year olds had repeat scanning in Newcastle, and eleven 3 year olds had repeat scanning in other regions.

Statistical methods

Confidence intervals for the proportion of children developing new scars were calculated as recommended by Blyth.[16] We were interested only in how large these proportions can get, so we calculated one sided 95% confidence intervals.

Results

Patients

Table 1 shows the number of children who attended for scanning and details about previous infections in all the children invited. Only seven families knew that their child had had another urinary infection and yet declined scanning. In each group about 97% of the invited children were either scanned (more than 80%) or were confidently believed not to have had another urinary infection (confirmed by the general practitioner). One child in the group of 3 year olds had died at 6.4 years awaiting a bone marrow transplant and had no renal scarring at postmortem examination.

Although more than a third of the families had moved house since the original scan (table 2), we were able to contact most of them, including three families living abroad who confirmed that their children had had no further urinary infections. Only two families in the group of 3 year olds (both abroad) and three families in the group of 4 year olds (two abroad, and one a travelling family) were untraceable.

The children who returned for scanning were similar for the two age groups (table 3). Girls outnumbered boys by about four to one. At initial referral similar proportions in each group were inpatients, had a diagnosis based on urine culture, and had recurrent infections. Of the children who returned for scanning, a similar proportion in each group reported further urinary infections, and an infection was diagnosed in several children at attendance. The children were scanned between their 6th and 15th birthdays, after an interval of 2.2 to 10.8 years.

Normal scans

The distribution of radioactivity between the kidneys was unavailable for 27 of the original scans and could not be assessed in one child with a horseshoe kidney. In the other 322 children without scars, the mean isotope uptake by the left kidney increased from 49.7% at the original scanning to 50.5% at the repeat scanning (at mean ages 4.1 and 9.6 years). The 3rd and 97th centile values for uptake by the left kidney were 41% and 59% for the original scan, and 42% and 62% for the repeat scan. The median differences between individual pairs of scans were 1% (SD 2.6%), and for 3rd and 97th centiles −5% and 6%.

Scarred kidneys

Five girls in the 3 year old group and none of the children in the 4 year old group had one or more scars on

one kidney at repeat scanning. All were aged under 3.4 years at the original scanning. The scarring was unequivocal, and the changes in isotope uptake by the left kidney were − 10%, − 9%, 13%, 16%, and 16% (outside the range for unscarred children). All had ultrasound confirmation of parenchymal thinning and calyceal clubbing (also shown in one case by urography). Micturating cystography in three of the children showed vesicoureteric reflux on the side of their scarring; one child refused the procedure, and another had a negative study at the age of 4.8 years (but had no upper tract imaging then).

Analysis of proportion of children developing a scar

As 5/209 children in the 3 year old group and 0/220 in the 4 year old group were scarred, the point estimates of the proportions scarred were 0.024 and 0 respectively. A difficulty in analysing the results is that for both age groups a substantial proportion of parents or children refused permission for repeat scanning. To assess the potential effects of this, we conducted a sensitivity analysis in which alternative confidence intervals were reported, where we assumed that in each age group either one or two of the unscanned children were in fact scarred (table 4). The reasons for these assumptions are as follows. Most of the unscanned children (28/33 of the 3 year olds and 34/41 of the 4 year olds) had no evidence of further urinary infections, and these children were highly unlikely to have developed scars. Therefore, our main uncertainty was focused on the three 3 year olds and the four 4 year olds who had evidence of further urinary infections but for whom permission for repeat scanning had been refused. However, it would be much too pessimistic to assume that all these seven children were scarred, considering that among the 48 children in the 3 year old group and the 55 children in the 4 year old group who had had further urinary infections and repeat scanning, only 4 and 0, respectively, exhibited scars.

Discussion

We have shown that among 3 year old children who have already had a urinary infection the proportion of those developing new scars may be as high as 5%. Despite no new scars among the 220 children in the 4 year old group, 1% of this group could develop them. If only one of the unscanned children had a scar, this figure would rise to 2%. To reduce the upper confidence limit to 0.5% we would have to study 600 children and still observe no new scars; to reduce the limit to 0.1% would require 3000 children.

The concept that the risk of developing a first pyelonephritic scar is low or non-existent from the age of 4 years onwards is likely to be supported[13 14] or refuted by case reports of children in whom scarring is identified by DMSA scanning, similar to the evidence from intravenous urography that purported to show a much older limit.[3-9] Because urography may take years to show scars that are immediately apparent with DMSA scanning,[10-12] the late onset "new" scars previously described are likely to have started to form before the age of 4.

A widely accepted model of reflux nephropathy warns that permanent scarring can occur after only a brief urinary infection in the presence of vesicoureteric and intrarenal reflux.[17] It is not clear why children become (presumably gradually) less vulnerable to scarring as they get older: vesicoureteric reflux tends to resolve; parenchymal maturation might be relevant; it may simply be a question of probabilities—perhaps vulnerable segments of the kidney scar early on. When investigated after a urinary infection, 6.7% (one sided 95% confidence interval 0% to 9.9%) of children aged under 4 years with vesicoureteric reflux also had intrarenal reflux, whereas none (0% to 2.0%) of the older children did.[18] Whatever the mechanism, it is biologically implausible that the risk falls suddenly at a precise age.

Reaching a very low or zero risk of developing a new renal scar after the age of 4 years has important clinical implications. It is agreed widely that children should have imaging of their renal tracts after a urinary infection, including ultrasonography at any age and DMSA scanning either up to age 7 or up to any age.[2] Most members of the Royal College of Physicians's working group favoured urinary surveillance every three months for two years in children aged over 7 with a urinary infection and normal imaging[2]; the authors of studies based on urography advise monitoring until age 10 or 15.[4 6] Our data suggest that a child aged under 4 with normal imaging still has about a 1 in 40 risk of developing a new scar and may do so without obvious urinary tract symptoms, so we also ask general practitioners to undertake surveillance until the children are aged four; we perform micturating cystography and repeat DMSA scanning in positive cases. Our data

Table 3 Details of children who had repeat scanning with dimercaptosuccinic acid (DMSA). Values are numbers (percentages) of children unless stated otherwise

Details	3 year olds	4 year olds	Children with scars (n=5)
Information available before repeat scanning			
Total	209	220	
Female	162 (78)	177 (80)	5/5
Initial referral as inpatient	29 (14)	34 (15)	0/5
Referral diagnosis based on urine culture	179 (86)	178 (81)	5/5
No of infections before original scanning:			
1	127 (61)	121 (55)	0/5
2	25 (12)	29 (13)	2/5
⩾3	7 (3)	16 (7)	1/5
Unknown	50 (24)	54 (25)	2/5
Age range at original scanning (years)	3.00-3.99	4.00-4.99	3.10-3.37
Information at time of repeat scanning			
Total	176	179	
No of infections between scans:			
0	128 (73)	124 (69)	1/5
1	22 (13)	8 (4)	
2	3 (2)	17 (9)	
⩾3	23 (13)	30 (17)	4/5
Infection at repeat scanning	7 (4)	24 (13)	2/5
Age range at repeat scanning (years)	6.04-13.99	6.97-14.28	9.12-11.32

Table 4 One sided 95% confidence intervals for proportion of children developing new scars

Assumption for No of scarred children among those not scanned	3 year olds	4 year olds
As observed	0 to 0.050	0 to 0.014
One extra	0 to 0.056	0 to 0.021
Two extra	0 to 0.062	0 to 0.028

Key messages

- Urinary tract infections can cause renal scars in young children that may lead to hypertension or renal failure, often years later
- Scars can be detected immediately on scanning with dimercaptosuccinic acid (DMSA) but may not be apparent for years if only intravenous urography is used
- Previous studies based on intravenous urography have suggested that new scars may develop in children up to the age of 10 years
- This study, which used DMSA scanning, shows that there is little or no risk of new renal scars developing in children aged 4 and older

suggest, however, that children with normal imaging after their fourth birthday need no surveillance and no further imaging of the upper urinary tract if they have another urinary infection.

Because urinary infection in childhood is common, this reduction in monitoring could lead to large financial savings and less inconvenience for children and their families. Our unit's referral figures,[19] closely similar to those from high recruitment studies,[20 21] show that 3.0% of children between their fourth and eleventh birthdays are referred with a urinary infection. If we undertook two years of urinary surveillance for those with normal DMSA scans, our unit would monitor an extra 553 children—which translates to 41 500 throughout the United Kingdom.

If the risk of a new scar after age 4 years is very small, but not zero, the rigorous application of these proposals could obscure that risk by creating a self fulfilling prophecy. It is important that management strategies for childhood urinary infection are continuously reviewed.

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Any questions

Does laser treatment offer a permanent cure for facial hirsutism in women?

Some women have isolated thick hairs growing on their faces and these can be effectively treated by any technique that can destroy a hair follicle. The most common method is electrolysis, but any procedure that destroys the hair root under the surface of the skin would be effective. The scar that develops at the site is small and invisible. Laser therapy is effective at destroying such hair growth.

Women with more profound beards present a more difficult management problem as extensive electrolysis over a period of years leads to a network of dermal microscars which eventually merge, causing a plucked skin pattern of visible scars. Damage can be reduced by using smaller electrical currents if the thick terminal hair shafts are miniaturised with antiandrogens such as cyproterone acetate before treatment. However, permanent cure is rare because there is continued stimulation of vellus hair by circulating androgenic hormones.

The question is, therefore, can laser destruction result in hair loss without scars and also prevent the continued stimulation of vellus follicles into large visible hairs? To date, the answer must be no. Laser destruction of hair follicles is still in its infancy. It has been reported only on fine hairs, which lie close to the skin surface rather than deeply set beard hairs, and only short term data are available. There is certainly an initial reduction in the number of hairs after treatment but after six months even an enthusiastic report states that "much of the hair has regrown."

There is currently no training programme for laser therapists. Although some local authorities have bylaws regarding the activities of cosmetic therapies, there is no formal need for licensing or regulation in Britain as it is unclear whether the law is competent to deal with this area (although this is actively under consideration by the Medical Devices Agency). In contrast, patients seeking electrolysis can rely on qualifications from formal training programmes such as that of the Institute of Electrology.

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