

Variability in the Interpretation of Dimercaptosuccinic Acid Scintigraphy After Urinary Tract Infection in Children

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Technetium-99m-dimercaptosuccinic acid (DMSA) scintigraphy is a frequently used diagnostic test in pediatric practice to assess the presence and severity of renal damage. Most commonly it is performed after urinary tract infection. The aim of this study was to investigate the variability in the interpretation of DMSA scans by pediatric nuclear medicine physicians in this clinical setting. **Methods:** We selected all 441 scans from children with first-time urinary tract infection who presented between 1993 and 1995 to a pediatric casualty department and who are participants in a prospective cohort study. Two hundred and ninety-four scans were performed at a median time of 7 days after diagnosis, and 147 scans were from children who were free from further infection over a 1-yr follow-up period. Two experienced nuclear medicine physicians independently interpreted the 441 scans according to whether renal damage was present or absent and using the modified 4-level grading system for DMSA abnormality of Goldraich. Apart from being informed that urinary tract infection was the indication for DMSA scintigraphy, no other clinical information was given to the nuclear medicine physicians. The indices of variability used were the percentage of agreement and the kappa statistic. For the grading scale used, both measures were weighted with integers representing the number of categories from perfect agreement. Disagreement was analyzed for children, kidneys and kidney zones. **Results:** There was agreement in 86% ($\kappa = 69\%$) for the normal-abnormal DMSA scan dichotomy, and the weighted agreement was 94% (weighted $\kappa = 82\%$) for the grading of abnormality. Disagreement of DMSA scan interpretation of ≥ 2 grades was present in three cases (0.7%). The same high level of agreement was present for patient, kidney and kidney zone comparisons. Agreement was not influenced by age or timing of scintigraphy after urinary tract infection. **Conclusion:** Two experienced nuclear medicine physicians showed good agreement in the interpretation of DMSA scintigraphy in children after urinary tract infection and using the grading system of Goldraich.

Key Words: technetium-99m-dimercaptosuccinic acid scintigraphy; urinary tract infection; renal damage; children

J Nucl Med 1998; 39:1428–1432

Renal cortical scintigraphy, using dimercaptosuccinic acid (DMSA), has become the reference standard for assessing renal damage (1–5). Although used for this purpose in a variety of clinical situations, the most common indication for DMSA scintigraphy in children is urinary tract infection (5). In this setting, DMSA is widely advocated to identify children who have associated renal damage (1–5), and clinical decision making is often influenced by the DMSA scan result. For example, in children over 1 yr of age with normal renal tract

sonography, it has been recommended that, if DMSA scintigraphy is normal, micturating cystourethrography is unnecessary (6–9). Others have recommended that chemoprophylaxis be given if a DMSA scan is abnormal at the time of urinary tract infection (3,10). A suggested indication for reimplantation surgery in children with vesicoureteric reflux who are receiving antibiotic prophylaxis is the DMSA detection of a new area of renal damage (10). Children with normal renal tracts and a normal DMSA scan are often discharged without further follow-up.

In each of these cases, patient care decisions depend on the accurate detection of renal damage and the reliable reporting of the DMSA scan images. The accuracy of DMSA for the detection of acute and chronic renal damage has been established by several animal models in which DMSA was compared with the reference standard, histopathology (11–15). Interpretation of the DMSA images is undertaken by medical practitioners, who in most instances are nuclear medicine physicians. If DMSA scintigraphy is a reliable test of renal damage, the same image will be interpreted in a similar manner by two different physicians, and patient management decisions will, therefore, not differ significantly, depending on which physician interpreted the scan. If, however, there is considerable disagreement in the interpretation of the same DMSA scan by experts, then DMSA scintigraphy may not be a reliable test for renal damage and caution should be exercised in basing clinical decision making on the reported results.

Despite the widespread use of DMSA scintigraphy in pediatric practice, the extent of variability in interpretation by nuclear medicine physicians has not been examined in detail. There have been three previous studies (16–18), with a total of 173 scans, but none measured agreement beyond chance in the DMSA diagnosis of damage by two or more observers. We investigated the extent and possible sources of variability in DMSA scintigraphy interpretation by two experienced nuclear medicine physicians.

MATERIALS AND METHODS

Case Selection

Broadly, two groups of children have DMSA scintigraphy after urinary tract infection: children who are scanned shortly after presentation (in whom renal damage may be pre-existing or represent acute pyelonephritis) and children who are scanned after the acute damage has resolved (in whom renal damage may predate the index infection or may be postinfective).

Cases were drawn from a prospective hospital-based cohort study of children under 1 yr of age with their first documented urinary tract infection to match this spectrum of patients. Of 304 eligible children, 295 children had DMSA scintigraphy performed

Received May 8, 1997; revision accepted Oct. 23, 1997.

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within 4 wk of presentation (early DMSA) between March 1993 and December 1994. In 1 child, technical difficulties with radio-labeling resulted in no image being evaluable. As part of the follow-up program, 173 children had repeat DMSA scintigraphy performed 1 yr later (late DMSA). The remainder had elected not to participate in the longitudinal component of the study. One hundred and forty-seven children (84.9%) had not had a proven symptomatic urinary tract infection during the intervening period. The DMSA scintiscans of both the early and the late groups (442 scans total) were used as cases.

Institutional ethics approval had been obtained for the cohort study, and informed consent was obtained from the parents of children who participated.

Participating Nuclear Medicine Physicians

The two nuclear medicine physicians on the staff of the New Childrens' Hospital were invited to participate. Both are nuclear medicine physician specialists, have 15 yr of clinical experience reading DMSA scans and interpreted 370 DMSA scans in 1995. The percentage of time spent reading DMSA scans in clinical practice was 13% for both nuclear medicine physicians.

Data Acquisition

For this study, both nuclear medicine physicians independently reread all eligible DMSA scintiscans between September 1995 and May 1996. This was 3–38 mo after the scan had been performed by the nuclear medicine department and reported by either physician as part of his routine clinical practice. It was not feasible to blind the nuclear medicine physicians to the objectives and design of the study. Apart from knowing that the indication for the scan was urinary tract infection, no clinical information or results of other renal tract imaging were given to the physicians.

The technical aspects of DMSA scintigraphy did not change during the period. A dose of 40–120 MBq DMSA was injected intravenously, after adjustment for body weight. Planar anterior, posterior and right and left posterior oblique 4-min images of both kidneys (150,000–200,000 counts) were obtained 3 hr postinjection using a General Electric Starcam 400ACT or 4000IXCT gamma camera (GE Medical Systems, Milwaukee, WI) with high-resolution collimators. A DMSA scan was defined as abnormal if a defect in renal contour or an area of relative photon deficiency in the renal cortex was present. The defects were localized to three regions of the kidney (midzone, upper pole and lower pole) or were reported as diffuse if generalized photon deficiency was evident throughout the kidney. The scintiscans were also graded according to the severity of the abnormality using a modified system of Goldraich (19): Grade I, no more than two cortical defects; Grade II, more than two cortical defects but remnant areas of normal renal parenchyma; Grade III, diffuse reduction in uptake of DMSA throughout the whole kidney with or without focal defects; and Grade IV, shrunken kidney contributing <10% of the overall renal functional mass.

All scintiscans were displayed on radiographic film. An identical checklist was used by both nuclear medicine physicians to record their observations, which was reviewed with them before the study commenced. The nuclear medicine physicians were asked to interpret the images as they would in their usual clinical practice, and no external time restraints were imposed.

Data Analysis

Interobserver variability in the interpretations of the 441 DMSA scintiscans was assessed from the readings of both nuclear medicine physicians. The measures of variability used were the percentage of agreement (20) and the kappa statistic (21), with kappa also expressed as a percentage. The kappa statistic is the preferred test of agreement because it measures agreement beyond that expected

TABLE 1
Results of Two-Observer Reporting of 441 Dimercaptosuccinic Acid Scans in Young Children with Symptomatic Urinary Tract Infection: Agreement on Individual Scans

	Observer 2				
	Normal	Grade I	Grade II	Grade III	Total
Observer 1					
Normal	259	23	2	0	284
Grade I	35	73	6	0	114
Grade II	0	9	12	3	24
Grade III	1	0	3	15	19
Total	295	105	23	18	441

by chance alone. For the ordinal grading scale used, both measures were weighted with integers representing the number of categories from perfect agreement (22,23).

Variability was assessed at three levels: patient, kidney and kidney zone (upper pole, mid pole, lower pole and diffuse). Of the three options, disagreement in the interpretation of patient scans was regarded as the most clinically important. For this analysis, patients were assigned to the group corresponding to the maximal grade of abnormality for either kidney. That is, if a difference in interpretation of side or location of cortical defect occurred, the management implication would be less than if a DMSA scintiscan was reported as normal by one physician and abnormal by another. Because other clinical decisions are based on the DMSA result of individual kidneys, variability of interpretation for individual kidneys was also measured. This would be relevant if unilateral ureteric reimplantation was considered because of the development of a new DMSA scan defect. Disagreement in kidney zone interpretation was also analyzed, corresponding to individual lesions.

Potential Sources of Variability

Because the DMSA appearance of renal parenchymal abnormality at the time of urine infection may differ from the appearance of chronic or postinfective renal damage (2,3), the timing of DMSA scintigraphy may influence the variability of scan interpretation. Agreement was therefore calculated for the early (acute infection) and late (1 yr after infection) groups and then compared.

Because DMSA is primarily a proximal tubular agent (24,25), relative tubular dysfunction or immaturity may result in a poor-quality scintiscan (3,26) and, therefore, increase the probability of reporting variability. This hypothesis was tested by comparing variability for scintiscans for children <6 and ≥6 mo of age.

RESULTS

Cases

Scintiscans of all 441 cases were available for reading. The median time period between diagnosis and DMSA scintigraphy was 7 days (range 1–34 days) for the early acute infection group and 12.7 mo (range 5.3–26.7 mo) for the late postinfection group. The median age at DMSA scintigraphy for all patients was 14.8 mo (range 0.4–72.2 mo). There were no cases of Grade IV abnormality.

Observer Variability

The observations and variability in reading are shown in Tables 1–3. Figure 1 shows a DMSA scan of a patient for which there was perfect agreement on location and grade of severity. Figure 2 shows a DMSA scan of a patient for which interpretations differed. Observer 1 interpreted the scans of 284 children (64.4%) as normal. Observer 2 interpreted the scans of 295 children (66.9%) as normal. The percentage of agreement was 86% when each patient scan was classified as normal or

TABLE 2

Results of Two-Observer Reporting of 441 Dimercaptosuccinic Acid Scans in Young Children with Symptomatic Urinary Tract Infection: Agreement on Individual Kidney Scans

	Observer 2				
	Normal	Grade I	Grade II	Grade III	Total
Observer 1					
Normal	660	36	2	1	699
Grade I	43	84	6	0	135
Grade II	1	9	17	3	29
Grade III	2	0	3	15	22
Total	706	129	28	19	882

abnormal, with a weighted agreement of 94% for grade of abnormality. The corresponding kappa values were 69% and 82%, respectively. There were three cases (0.7%) in whom the reported grades differed by 2 or more. Interobserver agreement did not vary appreciably according to whether patients, kidneys or kidney zones were reported.

Possible Sources of Variability

Disagreement was no more likely to occur in children ≤ 6 mo of age than in those ≥ 6 mo of age (Table 4).

TABLE 3

Dimercaptosuccinic Acid Scan Interpretation Variability for Young Children with Symptomatic Urinary Tract Infection

Comparison	Agreement		Kappa (%)	
	%	95% CI	κ	95% CI
Patients				
Normal/abnormal	86	83-89	69	62-76
Grade of abnormality*	94	92-95	82	77-88
Kidneys				
Normal/abnormal	90	88-92	70	64-76
Grade of abnormality*	96	95-96	80	75-86
Kidney zones				
Upper pole	93	92-95	75	68-81
Mid pole	97	95-98	74	65-83
Lower pole	93	92-95	71	63-78
Diffuse	99	98-99	73	59-87

*Weighted kappa and agreement with integers representing the number of categories from perfect agreement.

95% CI = 95% confidence intervals.

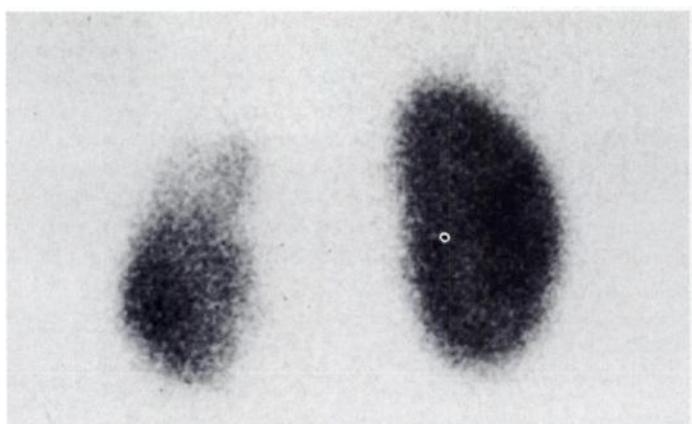


FIGURE 2 Example of DMSA scan for which there was variability of interpretation. Both observers reported this scan as showing multiple focal cortical defects in the upper and lower poles of the left kidney (posterior view) or at least Grade II, but one observer reported this as Grade III because the intervening renal parenchyma was not regarded as normal, i.e., diffuse parenchymal abnormality.

Agreement of scan interpretation did not vary appreciably depending on the time of scintigraphy after urine infection (Table 4). In contrast, the kappa value was relatively low for the post-urinary tract infection group, which can be attributed to the lower mean prevalence of DMSA scan abnormality in this group (27). The mean prevalence of DMSA scan abnormality for the acute infection group was 42.9% (observer 1 = 44.9%, observer 2 = 40.8%), and the mean prevalence of DMSA scan abnormality for the postinfection group was 17.4% (observer 1 = 17.0%, observer 2 = 17.7%).

After completion of all reporting, both nuclear medicine physicians also met to review specific scintiscans chosen as examples of disagreement and to comment on possible reasons for variability of reporting. Four sources of variability were identified. First, in some cases, the scintiscan was technically suboptimal, and the images were blurred. This occurred in newborn infants due to poor uptake and in children who moved while the image was being obtained. The extent to which there was adjustment for this poor image quality in the interpretation of perceived scan abnormality varied with the observer. For example, if there was blurring of the image due to patient motion, one observer remarked that he was less likely to interpret an area of relative photon deficiency as a cortical defect. Second, interpretation of scan appearances differed when the perceived abnormality may have been due to normal



FIGURE 1. Example of DMSA scan for which there was perfect agreement on location and grade of abnormality. Both observers reported this DMSA scan as showing multiple cortical defects in the left kidney (posterior view), i.e., Grade II abnormality.

TABLE 4
Potential Sources of Variability in Dimercaptosuccinic Acid Scan Interpretation Variability for Young Children with Symptomatic Urinary Tract Infection

Comparison	Agreement		Kappa (%)	
	%	95% CI	κ	95% CI
Age at time of scintigraphy*				
<6 months	86	80-93	73	60-85
≥ 6 months	85	80-91	69	59-80
Timing of scintigraphy after urinary tract infection				
Acute infection (<1 month)	81	76-85	71	63-79
Postinfection (>12 month)	83	77-89	55	37-73

*Abnormal/normal DMSA scan outcome and for children with DMSA scintigraphy performed within 1 mo of urinary tract infection.
95% CI = 95% confidence intervals.

or exaggerated anatomic structure, such as the pelvicalyceal system. Third, in some cases the same abnormality was perceived differently. For example, one physician regarded renal parenchyma between focal defects as normal and the other regarded it as abnormal, but both commented that they "saw what the other was seeing." Fourth, one nuclear medicine physician saw a cortical defect that was missed by the other, who noticed the defect when the scan was reshowed, and vice versa.

DISCUSSION

This study has demonstrated a high level of agreement in the interpretation of DMSA scans of children presenting with urinary tract infection by two experienced nuclear medicine physicians. The kappa value for the normal/abnormal dichotomous result was 69%, which has been classified as good (21) or substantial (20) agreement. In 14% of children, there was a clinically important difference in interpretation, with one physician interpreting the DMSA scan as normal and the other as abnormal, although the reported grade only differed by 2 or more in 0.7%. The overall level of agreement and kappa were similar whether patients, kidneys or kidney zones were compared. The clinical implication of these findings is that the management of children or individual kidneys after urinary tract infection is not appreciably altered, regardless of which experienced nuclear medicine physician interprets the DMSA scintiscans.

These data compare very favorably with most diagnostic tests. In a recent study of the variability in 10 radiologists' interpretations of 150 mammograms for the diagnosis of breast cancer, there was a median percentage of agreement of 78% and a median weighted kappa of 47% (28). The kappa of 69% in our study is similar to that (77%) of a recent comparative study of the interpretation of 205 extremity radiographs for the diagnosis of fracture by a pediatric radiologist and the treating emergency physician (29).

This study has also demonstrated a high level of weighted percentage of agreement for the severity of DMSA scan abnormality using the grading system of Goldraich (19). The weighted percentage of agreement was 94% for patients and 96% for kidneys. The corresponding kappa values were 82% and 80%, respectively, which are regarded as almost perfect (20) or excellent (21). Several different grading systems for DMSA renal parenchymal abnormality have been proposed (30–33), but none has been consistently used by several centers. This probably reflects the uncertain clinical significance of classifying patients and kidneys according to severity of damage. We have adopted a modified grading system of Goldraich (19), which, in turn, is based on the intravenous urography schema formulated by Smellie et al. (34). Although originally suggested as a grading system for renal scarring, we have also graded kidneys at the time of infection, which, in some cases, will represent changes due to acute infection. We have done this to establish the prognostic significance of the different grades of DMSA scan abnormality at the time of urinary tract infection in a prospective study, and because we do not believe that the progression of abnormal areas on DMSA scintigraphy is sufficiently well established to differentiate scars, acute infective changes and pre-existing damage, which may be congenital in some cases. These data show that there is a very high level of agreement using this grading system to classify DMSA scintiscans in children after urinary tract infection.

The evidence from animals that DMSA accurately localizes acute pyelonephritis and postpyelonephritic scarring is compel-

ling. Depending on the histologic definition of pyelonephritis used, the sensitivity and specificity of DMSA for the diagnosis of urinary tract infection-related renal damage are 80%–89% and 93%–100%, respectively (12–15). Equivalent studies in humans are not possible. In humans, many comparative studies have been undertaken using intravenous pyelography as the historical standard for renal parenchymal abnormality, DMSA scintigraphy and renal ultrasonography (16,35–39). It is concluded usually that DMSA is the most sensitive and specific imaging modality for detecting renal damage in children. These conclusions are somewhat empirical, because in no case has the gold standard, histopathology, been used. Certainly, comparisons between the imaging modalities can be made in terms of how many renal cortical defects are detected using each imaging modality, although the clinical significance of these differences has yet to be established. Because DMSA misclassifies a small proportion of patients and is therefore not a perfect standard, the commonly used measures of test performance, such as sensitivity and specificity, will be distorted when used as a reference standard against which other tests are compared. Approaches to this problem have been discussed previously (40).

In addition to assessing a new diagnostic test against the current reference standard, its validity needs to be established by ensuring that there is acceptable agreement in the interpretation of the test results by different observers (27). DMSA has been used widely for the diagnosis of renal damage in children, particularly for urinary tract infection, since the mid-1980s (1–4). Despite this, an adequate study of variability in DMSA interpretation has not been conducted previously. We were only able to find three published studies that have assessed DMSA interpretation variability (16–18). In a study of DMSA, intravenous urography and ultrasonography in 27 children at risk for renal scarring, the percentages of agreement in DMSA scan interpretation for three observers were 90% and 95% for interobserver and intraobserver comparisons, respectively, but no details of how these values were determined were given, and no kappa statistic was calculated (16). The percentage of agreement does not take into account chance agreement between observers and is, therefore, a poor measure of variability (20–23,27). Another study, published in abstract form (18), was designed to assess interobserver DMSA reporting variability in 165 kidneys (83 scans) among experienced radiologists and nuclear medicine physicians from four different centers. In 72% of cases (118 of 165), there was perfect concordance of reporting, which included precise localization of the abnormality. Disagreement at the level of the patient and kidney, which are more important for clinical decision making, were not given, nor was any assessment of chance agreement calculated. In the only study of DMSA interpretation variability with adjustment for chance agreement, the scans of 63 children at risk for renal parenchymal abnormality were reported by two nuclear medicine physicians using a 6-category classification system: contour, location, degree of photopenia, shape of defects, overall impression and percentage of kidney involvement (17). Percentage of agreement (74%–95%) and weighted kappa (40%–70%) varied considerably with the DMSA scan feature reported. Prior evidence that there is a clinically acceptable difference in DMSA scan interpretation by two or more observers has, therefore, been lacking.

The circumstances of this study may limit the extent to which our conclusion applies to other settings. Both nuclear medicine physicians who interpreted the images were experienced, well trained and belonged to the same department. Agreement may well be lower if DMSA scan interpretation is compared across

nuclear medicine departments in different geographical locations and among nuclear medicine physicians who have different levels of experience. Our results may, therefore, represent the maximal level of agreement. Additional studies are required to appropriately assess physician experience and center effects on the variability of DMSA scan interpretation.

Since this study was completed, SPECT and pinhole-collimated DMSA imaging have been introduced into clinical practice. Although the methods described in this study for the assessment of physician perception of DMSA images are as applicable for SPECT and pinhole-collimated DMSA as they are for high-resolution collimated DMSA with planar images, the specific findings of this study may not be. The degree of variability in physician interpretation of SPECT and pinhole-collimated DMSA is currently not known.

CONCLUSION

Relative to most diagnostic tests, we have demonstrated a high level of agreement in the interpretation of DMSA scintigraphy after urinary tract infection. The results of this test provide a firm basis for medical decision making by physicians who care for children with possible renal parenchymal abnormality.

ACKNOWLEDGMENTS

This study was supported by National Health and Medical Research Council Project Grant 960806, the Children's Hospital Fund and the Manildra Group of Companies. We acknowledge the kind assistance of the Department of Nuclear Medicine technical and secretarial staff, particularly Glenda Parsons, the chief technologist.

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