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Use of serum free light chain analysis and urine protein electrophoresis for detection of monoclonal gammopathies

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Abstract

Background: Serum free light chain (FLC) analysis is used in the prognostic assessment and monitoring of patients with monoclonal gammopathies (MG). Its use in detection of MG is less widespread despite good sensitivity for diseases poorly detected by serum protein electrophoresis (SPE), e.g., FLC disease and AL amyloidosis. FLC analysis may facilitate earlier diagnosis in these diseases. However, if replacing urine protein electrophoresis (UPE) in an initial screening algorithm, this must be balanced against any loss of detection of Bence Jones proteinuria (BJP).
Methods: We assessed the effect of replacing UPE with FLC. Sensitivity of FLC for BJP was assessed in 126 clinical cases where UPE and FLC analyses were performed. Impact on disease detection was assessed from 753 patient sera tested by SPE and FLC and 128 patients matched associated urine samples.
Results: Sensitivity of FLC for BJP was 98%. Use of FLC in routine testing increased the number of MG detected by 7%.
Conclusions: Using FLC alongside or in place of UPE can give clinical benefit through earlier diagnosis and hence treatment earlier in the patients' disease.
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Keywords: Bence Jones protein; monoclonal gammopathy; paraproteinaemia; serum free light chain; serum protein electrophoresis.

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Introduction

A growing number of studies report the use of serum κ and λ free light chain (FLC) analysis in the diagnosis (1–4), prognosis (5–7) and monitoring (8–13) of monoclonal gammopathies (MG) (14, 15). Attention has been focused on the replacement of urine protein electrophoresis (UPE) with FLC measurements in detection of disease (16, 17). This has two benefits, (i) a single serum sample may be used and (ii) poor patient compliance with urine testing is eliminated. The International Myeloma Working Group guidelines for serum-FLC analysis in multiple myeloma (MM) and related disorders recently stated that ''the serum FLC assay in combination with serum protein electrophoresis (SPE) and serum immunofixation is sufficient to screen for monoclonal plasmaproliferative disorders other than light chain amyloidosis'', although they are not specific as to how these should be used in practice (10). Disease outcome data, where FLC and the κ:λ ratio have been used in place of UPE, is limited to a few studies (16–18) with ongoing debates regarding interpretation (3, 15, 16, 19–21).

The aims of this study were (i) retrospective evaluation of the sensitivity of the FLC ratio for Bence Jones proteinuria in our patients; (ii) to report the outcome of our experience with the use of FLC and SPE in parallel.

Materials and methods

The Immunology Department, Hull Royal Infirmary (Hull, UK) provides a laboratory service including SPE, UPE and serum FLC assays for a population of 600,000 residents registered with primary and secondary care physicians. We routinely reflex test FLC when a new MG is detected, alongside the standard request for UPE. The results reported here were performed prospectively as part of our routine investigative protocols for these patients. This study was approved by the Hull and East Riding Local Research Ethics Committee.

Sensitivity of FLC ratio for urinary Bence Jones proteinuria (BJP)

We retrospectively analyzed data from a cohort of 496 patients who had a newly identified paraprotein [by SPE/UPE and immunofixation (IFE)] in samples received over a 15-month period. Serum and urine results were linked when these were performed within 90 days of each other.

UPE was performed by agarose gel electrophoresis (sensitivity 10 mg/L). Urine IFE (sensitivity <5 mg/L) was performed if a band other than albumin was noted. Both urine tests were performed according to the manufacturer's recommended protocols using the Sebia Hydrasys agarose gel system (Sebia UK, Camberley, UK).

Serum FLC analysis was performed according to the manufacturer's recommended method by a latex-enhanced immunoassay (Freelite, The Binding Site, Birmingham, UK) using a Beckman-Coulter IMMAGE nephelometric analyzer (Beckman Coulter, High Wycombe, UK). SPE was performed by either the SEBIA Hydrasys gel system, or Capillarys 2 (Sebia UK, Camberley, UK), according to the manufacturer's recommended protocols.

Routine use of FLC in parallel with serum protein electrophoresis

A cohort of 753 serum samples submitted for plasma cell dyscrasia screening over a 10-week period underwent SPE and FLC testing. SPE was performed by capillary zone electrophoresis (CE) (Capillarys 2, Sebia UK, Camberley, UK) and serum FLC was performed using a latex-enhanced immunoassay as above, but with an additional check for antigen excess by repeating all FLC samples at a 1:24 pre-dilution. When a urine specimen was available for a patient, UPE was also performed by CE on the same system and IFE if the UPE was abnormal. Serum samples with an abnormal SPE or with an abnormal FLC ratio were reflex tested by IFE (SEBIA Hydrasys). Repeat samples were requested from patients who had an FLC ratio outside the reference interval (0.26–1.65) (22), but within 3.5 SD of the mean (i.e., 0.18–2.01) before referral, if no other abnormality was present. These repeat samples were considered normal if they fell within the reference interval. An immediate hematology referral was recommended if the FLC ratio was >3.5 SD from the mean. The Binding Site Ltd. (Birmingham, UK) provided Freelite kits free of charge for this part of the study.

Results

Sensitivity of FLC ratio for urinary Bence Jones proteinuria

Of 496 newly diagnosed MG patients, monoclonal paraprotein was detected by SPE in 98% of cases (488 patients). In the remaining 2% (eight patients), the paraprotein was only detected by UPE. Urine samples were received from 30% of patients within 7 days of assessment of the serum sample, an additional 9% by 30 days and a total of 57% (281 patients) within 90 days. No urine sample was received from the other 281 (43%) patients within 90 days of the serum sample. A paraprotein was detected in 54% (151 of 281) of the urines received. Many of these urine samples were only received following a reminder notice from the laboratory of the outstanding UPE request, or during hematology follow-up.

Urinary FLC was detected in 83% (126 patients) of urine samples containing a paraprotein, and in 59% (89 patients) it was the sole paraprotein in the urine. One hundred and twenty-four patients had a serum FLC outside the reference range; the majority of them (n = 119) had values outside the 3.5 SD range. Both of the remaining two patients with normal FLC ratio had IgG-κ paraproteins, detected by SPE, with an IgG-κ and smaller free-κ band in the urine. The serum and urine samples were obtained on the same day for one of these patients, and with a time span of 20 days for the other. BJP concentrations by densitometry were <50 mg/L and 100 mg/L, respectively.

Routine use of FLC in parallel with serum protein electrophoresis

During the period of the study, 753 sera and 128 urine samples (representing 17% of the sera) were received for analysis from patients with no previous history of a MG. Fifty nine of the urine samples (46%) were collected on the same day as the serum sample, a further 38 (30%) within 1 week, and 26 more (20%) within 1 month. Only five urine samples (4%) were collected more than 1 month (but within 90 days) of the serum sample. Figures 1 and 2 show the outcomes for these patients in relation to the FLC result. Of 636 patients with a normal CE, 46 patients had an abnormal FLC ratio. Follow-up of these 46 individuals identified two additional MM cases and three additional monoclonal gammopathy of uncertain significance (MGUS) cases (a 7% increase in the number of new diagnoses). No patient with BJP had a normal FLC ratio. In follow-up of 15 patients with normal urine CE and an abnormal FLC ratio, three patients had MGUS, two with concomitant renal failure (now known to cause a polyclonal increase in FLC and FLC ratio). At the time of this study, the renal reference range (23) had not been proposed. This is reflected by our finding of six patients with renal failure and an abnormal FLC ratio.

FLC assays helped to identify an additional five patients with a monoclonal lymphoproliferative disorder that were not detected by SPE alone. Urine samples were received from three of these five patients (at 2, 30 and 49 days after the serum sample).

Discussion

Sensitivity of FLC ratio for Bence Jones proteinuria

Our results show 98% sensitivity for the presence of BJP using a FLC ratio reference range of 0.26–1.65 (22); slightly higher than reported previously for unselected urine samples (3, 16, 17, 24).

Hofmann et al. (24) reported 97% sensitivity for 34 patients with BJP. The single patient that was missed was diagnosed with a probable polyclonal light chain on repeat urine sampling, giving a revised sensitivity of 100%. Hill et al. (17) studied the use of serum FLC in screening for monoclonal paraproteins and reported 85% sensitivity (11 of 13 BJP positive urines). Of two false negative results, one patient had an intact immunoglobulin MGUS, the other had no evidence of a B-cell disorder on bone marrow biopsy and skeletal survey. Both had very low BJP concentrations of about 50 mg/L. Katzmann et al. (3) performed a retrospective study of 428 consecutive positive urines that had monoclonal intact immunoglobulin and/or FLC present. They reported 86% sensitivity for patients with either of these monoclonal proteins in urine, rising to 93% sensitivity after exclusion of intact immunoglobulins. Beetham et al. (16) in a prospective study reported 76% sensitivity (26 of 34 patients), although as one of these patients was normal on repeat sampling, this may be interpreted as 79% sensitivity (26 of 33 patients). Of their seven patients with BJP and a normal FLC ratio, six

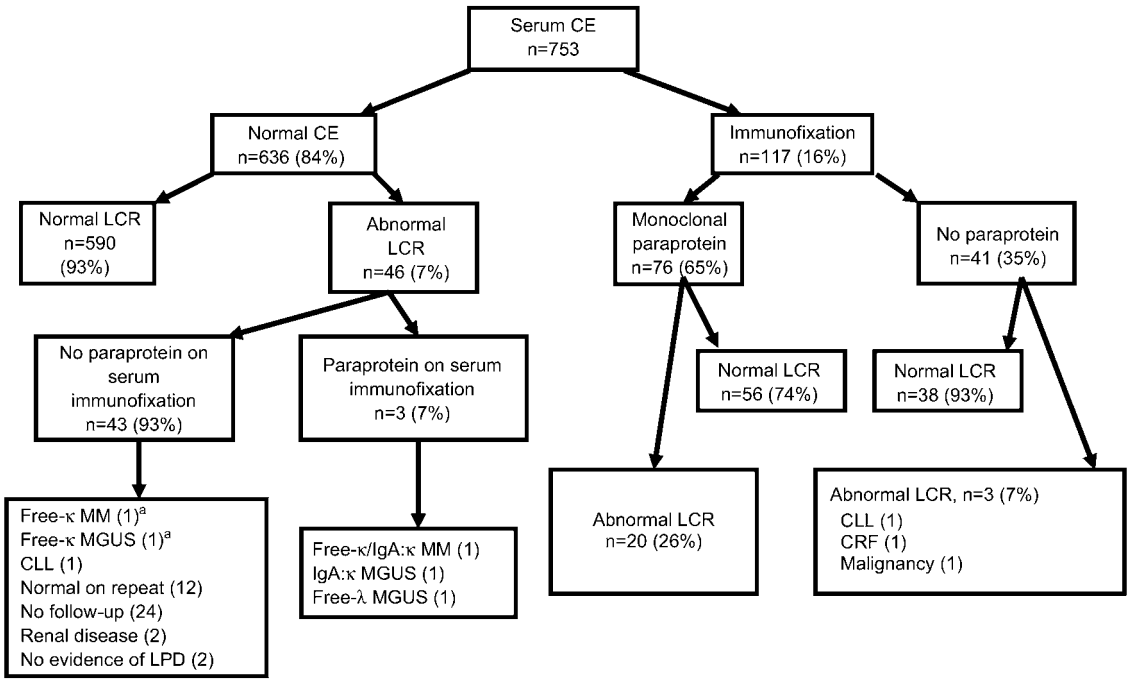

Figure 1 Screening outcomes from serum protein electrophoresis and serum free light chain ratio analysis.
[a]Monoclonal paraprotein visible on urine immunofixation but not by serum CE. Number of patients in parentheses. CE, capillary electrophoresis; LCR, serum free light chain ratio; MM, multiple myeloma; MGUS, monoclonal gammopathy of uncertain significance; CLL, chronic lymphocytic leukemia; LPD, lymphoproliferative disease; CRF, chronic renal failure.

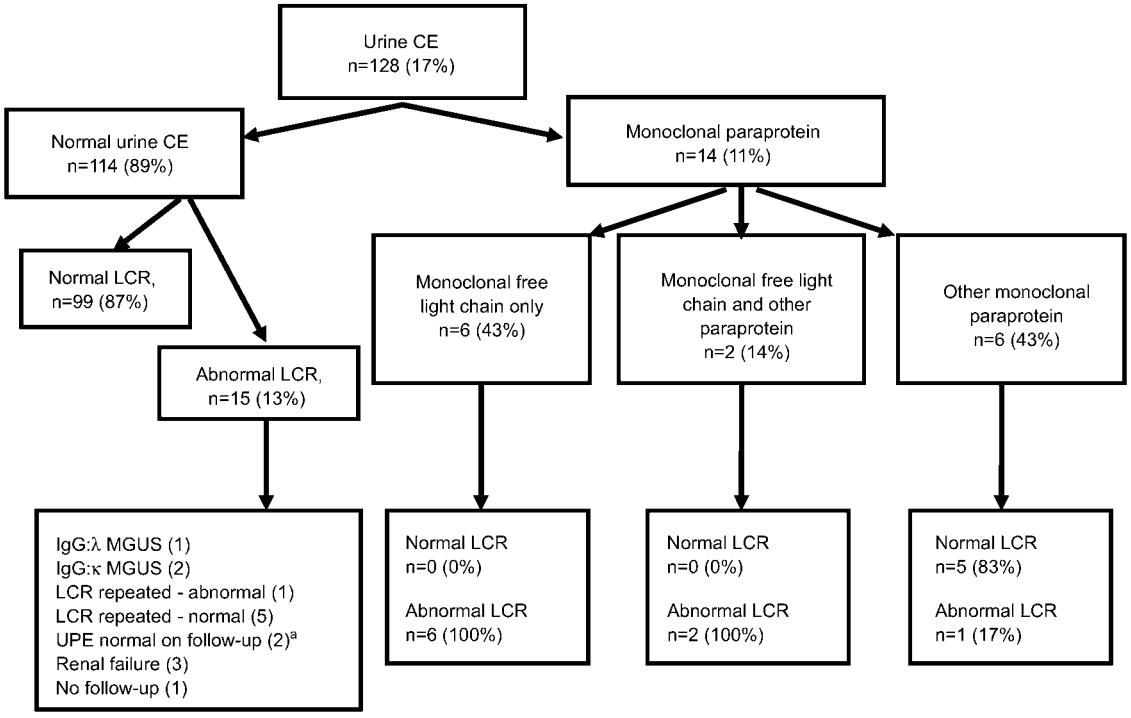

Figure 2 Outcomes from urine protein electrophoresis and serum free light chain ratio analysis.
[a]Repeat LCR not performed. Number of patients in parentheses. CE, capillary electrophoresis; LCR, serum free light chain ratio; MGUS, monoclonal gammopathy of uncertain significance; UPE, urine protein electrophoresis.

had an intact immunoglobulin paraprotein in the serum detected by SPE (3 MGUS, 2 MM and 1 non-Hodgkin's lymphoma). One patient was lost to follow-up. The urine BJP concentrations seen in these patients were all very low (30, <50, <50, 50, <75, 150, 150 mg/L), and in two there was a significant time lag between the serum and urine samples (57 and 83 days). Fulton and Fernando (25) found a sensitivity of 88%. In comparison, our data showed 98% sensitivity for BJP in a series of newly diagnosed MG. Combining these studies with weighting for study size gives an overall sensitivity of 92% (95% confidence interval 90%–94%).

These studies fall into two overlapping groups. Studies performing urine IFE for all urine samples report generally lower sensitivities (3, 16, 25) than those performing IFE only on urines with abnormal UPE [(17, 24) and this study]. The variation in reported sensitivity in these studies is probably due partly to these differences in study design. All studies used the same serum FLC assays, but urine IFE has higher sensitivity than UPE for BJP. Therefore, studies performing IFE on all samples detect more low level BJP and hence report lower sensitivity of FLC for BJP. Two of the studies do not specify the laboratory methods used for urine analysis (3, 24), but the study using IFE for all urines (16) showed lower sensitivity for FLC than the two studies using UPE and selected IFE [this study and (17)]. Use of concentrated vs. unconcentrated urine also affects sensitivity of UPE, and may be a significant factor in identifying samples for IFE in some studies [(17) and this study].

If the Freelite assay used in all of these studies was missing serum light chains of particular restricted epitope expression, the corresponding BJP concentrations should vary widely and not be exclusively low concentrations. There is one report in the literature of a demonstrable missed epitope (26), a problem now corrected (27). This suggests that the source of urinary light chains in these patients may not be directly from serum, but secondary to a kidney process, potentially involving breakdown of intact monoclonal paraproteins in some patients. If this is the case, these should be referred to as biological false positive results. Support for this view includes the high sensitivity of assays for light chain myeloma and AL amyloid, where analytical false negative results do not seem to be a major issue (4, 10, 14).

It is unlikely that false negatives are due to poor analytical sensitivity of the serum assays because FLC is detectable in serum below the renal threshold for overflow BJP (28).

Routine use of FLC in parallel with SPE

FLC has proven high sensitivity for light chain multiple myeloma (LCMM), AL amyloidosis, light chain deposition disease and non-secretory MM (4, 14), all diseases which often present with normal SPE and UPE, especially in the early stages of the disease when renal function is good. Our results confirm those of others, that use of the FLC ratio increases the detection of these disorders in clinical practice (4, 17).

Use of FLC in screening has the potential to identify a range of additional patients. Studies show that FLC ratio has excellent sensitivity for monoclonal light chain diseases: >99% for LCMM, 95% for AL amyloidosis, 92% for light chain deposition disease, and 73% for non-secretory myeloma (10, 14).

Hill et al. (17) and the data presented here show good agreement on the number of additional patients identified (12% and 7%, respectively), an overall average of 0.7% of all sera tested. The additional diagnoses found in these two studies include three patients with LCMM; an earlier diagnosis may help conserve patient renal function.

This study and others show that clinically significant additional or earlier diagnoses are achieved when FLC is used alongside or in place of UPE (17). Studies involving patients with BJP and normal FLC report only low levels of BJP and detection of the gammopathy by SPE in 78% of these patients (16, 17), with the remaining 22% being cases of FLC MGUS with very low urinary BJP which, as an isolated finding, is unlikely to affect clinical management. A recent study of four patients with monoclonal FLC demonstrated by urine IFE, but normal serum FLC ratio, did not quantify urine FLC (29). All four of these patients had a serum intact immunoglobulin paraprotein detected in serum. Subjective assessment of their published IFE images from concentrated urine shows very low urine light chain concentrations for some of these samples. In the context of AL amyloid, low level BJP is significant, but FLC has good sensitivity for this disorder (10, 14), and guidelines still recommend performing UPE when AL amyloid is suspected (10).

Any consequences of missed BJP can be mitigated by performing urine IFE. We suggest that an initial testing algorithm using SPE and FLC together, and reflex UPE testing for patients with a serum paraprotein, provides an excellent detection rate for BJP, including most low level BJP missed by FLC which are clinically important in AL amyloid. This approach has a higher sensitivity for BJP than that seen in previous reports (98% compared with 92%) and supports the recommendations in the Myeloma Working Group Guidelines (10).

A significant factor to be considered is the uptake/compliance of urine testing. In a study of 1027 newly diagnosed MM patients at the Mayo Clinic, 16% had LCMM with normal SPE and evidence of a monoclonal paraprotein seen only in the urine (30). If a urine sample is not analyzed, such patients will have a delayed diagnosis. Earlier diagnosis facilitates earlier intervention and the possibility of preserving renal function (31); we observed this scenario for two of our patients with MM and a normal SPE result. In our laboratory, only 17% of SPE requests have UPE performed within 90 days, lower than two other studies which reported 52% and 40% for patients in their cohorts (16, 17). We received urine sample requests on 57% of newly identified MG within 3 months of the serum sample. The UK National Pathology Benchmarking Review for 2007/2008 showed the number of UPE tests as a proportion of SPE at just 14% (298,392 sera from 47 laboratories; personal communication, D. Holland, February 2009). This probably underestimates the urine uptake as many SPE requests will be for monitoring known disease, when a lower frequency of UPE is required compared with SPE. The higher urine uptake seen in this

study and others (16, 17) may be related to patient follow-up after serum-based diagnosis and the research setting of each study. For patients presenting clinically with symptoms of an MG, a request for urine analysis is more likely. Nonetheless it is clear that many patients do not have appropriate urine testing performed.

The specificity of FLC for detecting disease should also be considered. UPE in combination with IFE is regarded as having very high specificity, i.e., having few false positives, reflecting the historical role of IFE as the gold standard screening methodology for detection of BJP. The studies reviewed above show a small number of false positives as a result of transient BJP or reporter error (16, 17). FLC specificity for B-cell dyscrasias, in this study and others, ranges from 95% to 98% (16, 17, 28, 32). The FLC reference interval has a direct effect on sensitivity and specificity and must be considered when developing local protocols. There is little evidence to support recommendation of invasive diagnostic procedures in patients with mild abnormalities of the FLC ratio and no other evidence of a monoclonal B-cell disorder. Conversely, a marked abnormality in the FLC ratio, even in the absence of other signs, warrants investigation by a hematologist. Action following detection of an abnormal FLC ratio will depend upon the degree of abnormality and the presence of other clinical and laboratory features.

When a choice must be made between FLC and UPE for testing, there is a clear advantage of FLC. It may be pragmatic to perform urine IFE for all patients with a new diagnosis of an MG as this will identify most missed BJP. However, in view of the very low urine BJP concentrations in these patients, this may be judged clinically unnecessary, unless AL amyloid is suspected (10).

Our use of FLC resulted in increased detection of significant disease. Diagnoses in these additional patients are clinically significant and include LCMM. Most missed cases reported in the literature are not true missed diagnoses because abnormal SPE was noted. What were commonly missed were low levels of BJP in patients with an MG evident by SPE. Review of our data and previous studies shows that FLC assays have excellent sensitivity for clinically significant FLC disease, and would improve screening outcomes if used either alongside or in place of UPE.

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Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. The supply of the assay and the employment or leadership played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.
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