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BIOMEDICINA - PATOLOGIA CLINICA - INFORMATICA

Proteinuria de Bence Jones

Protocolo Operativo para la determinación de la presencia de Proteínas de Bence Jones en Orina:

Propuesta y Relación Bibliográfica

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Introducción :

Las **Proteínas de Bence Jones (BJP)** son, por definición, **Cadenas Ligeras LIBRES MONOCLONALES (CLLM)**^{1, 5, 9, 11, 24, 35, 37}. Cuando en la bibliografía se emplean indistintamente, de manera inexacta y generando confusión, los términos Proteínas de Bence Jones, Cadenas Ligeras (Light Chains), Cadenas Ligeras Libres (Free Light Chains), Cadenas Kappa y Lambda, etc., se está en realidad haciendo referencia estrictamente a las Proteínas de Bence Jones.

Las **BJP** son indicadoras de un proceso maligno^{1, 2, 3, 4, 5, 6, 8, 9, 11, 15, 37, 38, 39}. **Su presencia está demostrada en el 60-87% de casos de Mieloma Múltiple (MM)**^{2, 4, 9, 22, 38} y, **en el 15-20% de los MM son el único producto biológico excretado por el clon maligno** (Mieloma Micromolecular, de Bence Jones o de Cadenas Ligeras)^{2, 4, 9, 21, 23, 38}.

Dada su fisiopatología, **su presencia es demostrable en la orina antes y con mayor facilidad que en el suero**^{21, 35, 36, 38}, excepto en caso de reducción del Filtrado Glomerular. Por ello, **en caso de sospecha de Gammapatía Monoclonal, es imprescindible estudiar la orina del paciente** pues puede demostrarse un componente monoclonal en ella, constituido por BJP, sin que se observe ninguna anomalía en el suero del mismo paciente.

Las **BJP** son, por ellas mismas, una “entidad maligna” que produce efectos patológicos principalmente en el **riñón**^{2, 4, 6, 8, 9, 13, 16, 17, 22, 25, 27, 28, 29, 30, 31, 32, 33, 34, 38}. Las BJP son nefrotóxicas y están estrechamente ligadas a las complicaciones renales del MM, en el que la 2ª causa de muerte es el fallo renal^{38, 40}. El daño renal es frecuentemente el primer síntoma que lleva al diagnóstico final del MM^{17, 26, 27, 38} y es además un factor pronóstico importante que influye en la supervivencia del paciente^{5, 14, 16, 20, 22, 27, 40}.

La determinación periódica^{2, 3, 4, 8, 38} de la **presencia y cantidad de BJP** presente en la orina es un elemento indispensable para el diagnóstico^{1, 5, 7, 9, 10, 11, 15, 24, 26, 36} (establecimiento de su estadio, etc.), el pronóstico^{2, 4, 7, 8, 9, 10, 11, 16, 17, 18, 20, 22, 26} y el control de la evolución y respuesta al tratamiento^{1, 2, 4, 5, 7, 8, 9, 11, 12, 15, 19, 22, 23, 37, 38} del **MM**.

La búsqueda de las BJP debe prever, para confirmar su composición, **el uso de un método inmunológico y**, para confirmar su distribución monoclonal, **el uso de un método electroforético**, además de tener presentes los siguientes hechos:

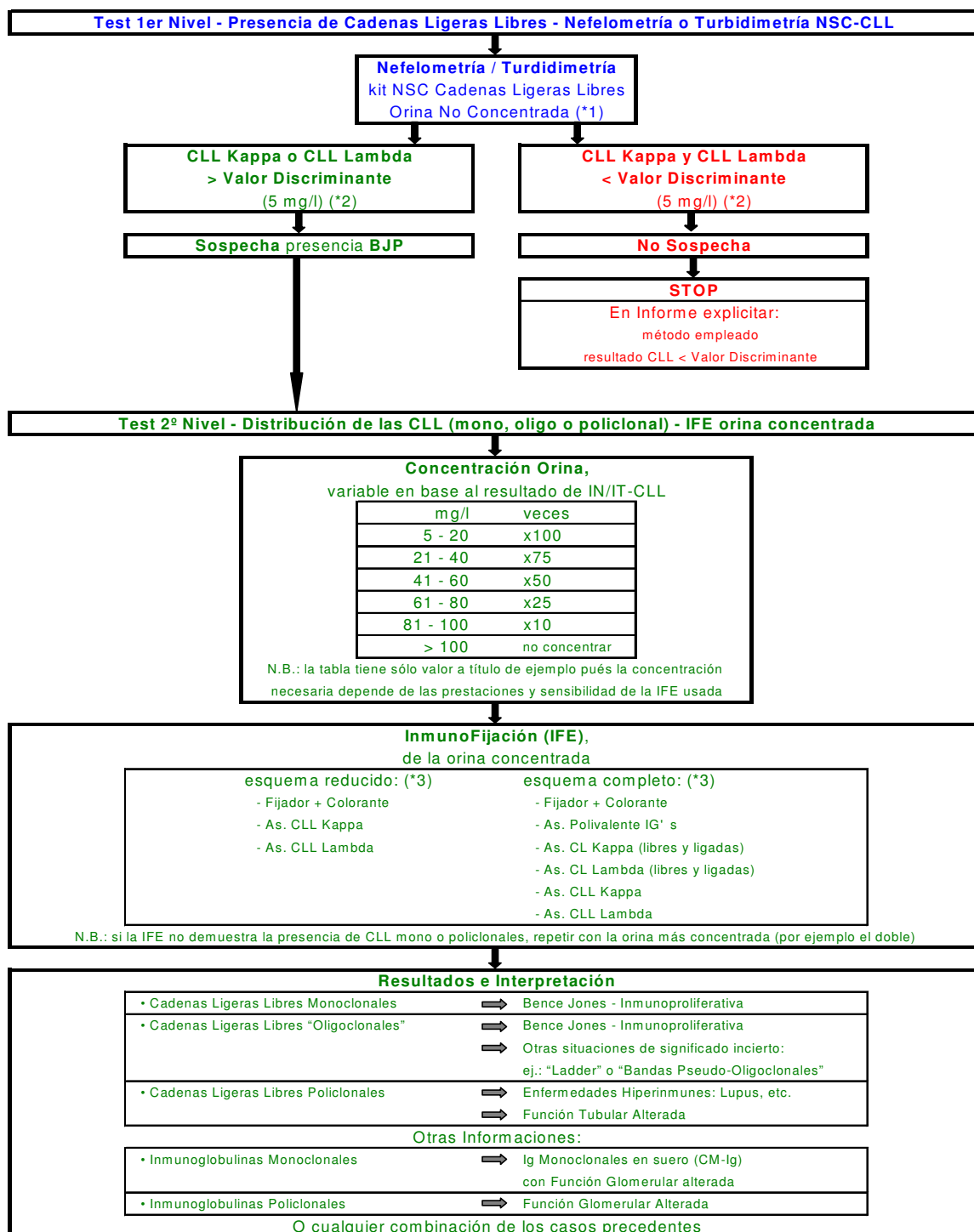
- 1.- Al estudiar la orina, podemos encontrar cualquiera de las siguientes proteínas, o una mezcla de ellas:
 - **BJP** (= CLLM)
 - Cadenas Ligeras Libres Policlonales (CLLP)
 - Cadenas Ligeras Libres Oligoclonales o “Ladders”
 - **Inmunoglobulinas Completas** (monoclonales y/o policlonales) (**IG's**)
- 2.- La presencia en la orina de **IG's completas** (acompañando a las BJP o solas) es bastante más **frecuente** de lo que generalmente se considera, en especial en pacientes con la función glomerular afectada.
- 3.- Los antisueros específicos **anti CLL** sólo reaccionan con las Cadenas Ligeras cuando estas no forman parte de las IG's completas, es decir cuando se encuentran **“libres”** (de ahí precisamente su nombre).
- 4.- Los antisueros **anti Cadenas Ligeras Totales** (libres + ligadas) (CLT) reaccionan con las Cadenas Ligeras tanto cuando están libres, como cuando están ligadas formando parte de las IG's, es decir **reaccionan** indistintamente con las CLL y **con las IG's completas**.
- 5.- Los factores anteriores tienen incidencia tanto en la determinación cualitativa de la presencia en la orina de BJP (=CLLM), como en su dosificación.

El protocolo operativo propuesto en la página siguiente prevé el uso de la Nefelometría (o Turbidimetría), con antisueros específicos anti CLL, como método inmunológico de primer nivel cuyo objetivo es evidenciar la presencia de CLL en la orina, y el uso de la Inmunofijación, también con antisueros específicos anti CLL, como método electroforético de confirmación cuyo objetivo es demostrar o descartar la monoclonalidad de las CLL antes evidenciadas. Al test de confirmación, Inmunofijación, se someterán sólo aquellas muestras que hayan resultado positivas al test de primer nivel, Nefelometría.

Propuesta Protocolo Operativo :

Esquema Protocolo

El protocolo operativo esquematizado a continuación es un ejemplo de como emplear el método de InmunoPrecipitación en fase líquida (Nefelometría o Turbidimetría) para la búsqueda de las Proteínas de Bence Jones en la orina, en una primera aproximación diagnóstica:



Nota (*2): u otro valor definido por el usuario

Notas

Nota (*1) - Tipo de Muestra :

Para el estudio de las CLL en general, y de las Proteínas de Bence Jones (BJP) en particular, se emplean distintos tipos de muestra sin que haya un acuerdo sobre cual resulta la más conveniente; las más comúnmente empleadas son:

- Orina de 24 horas
- Primera orina de la mañana
- Orina extemporánea; generalmente la segunda orina de la mañana

La muestra tradicional es la orina de 24 horas que, además de la valoración de la diuresis, permite promediar la presencia de las CLL de un período de tiempo razonable.

Algunos proponen el uso de una orina extemporánea, generalmente la segunda de la mañana, por su facilidad de obtención y porque es más difícil su contaminación, estimando la diuresis mediante la determinación de la Creatinina urinaria al objeto de descartar muestras demasiado diluidas que podrían dar Falsos Negativos. Esta propuesta presenta una mayor comodidad en la obtención y manejo de la muestra, pero no tiene en cuenta la muy probable producción cíclica de las CLL (apuntada por algunos autores, aunque no demostrada para las CLL pero sí para otras proteínas) que, dada su cortísima hemivida, determinaría también variaciones en su excreción urinaria que podrían llevar a que muestras cercanas al límite de sensibilidad de la metodología empleada pudiesen dar resultados falsamente negativos, además de dificultar la medida cuantitativa en este tipo de muestra incluso valorando la Creatinina como estimación de la diuresis. El uso de la primera orina de la mañana tampoco aporta nada nuevo respecto a otra orina extemporánea y además es más susceptible de contaminación.

Nuestra opinión es que hasta que no se demuestre lo contrario, y sobre todo si hay interés en la determinación cuantitativa, lo mejor es emplear la orina de 24 horas con Azida Sódica como conservante para prevenir una eventual contaminación bacteriana.

Nota (*2) - Valor Discriminante :

El valor discriminante propuesto en el protocolo, 5 mg/l (0,5 mg/dl), debe considerarse como una propuesta orientativa pues es el usuario quien debe determinar, de acuerdo con los clínicos y coherentemente con la sensibilidad de la metodología de confirmación empleada (usualmente IFE), el valor discriminante a emplear.

De cualquier modo, el valor propuesto (5 mg/l) es inferior a los valores relacionados en la bibliografía (por los pocos autores que se atreven a dar valores concretos) que coinciden en que resulta suficiente una sensibilidad de alrededor de 10 mg/l; es más *Beetham* llega a afirmar en las conclusiones de su artículo que "*todos los laboratorios deberían ser capaces de detectar BJP de alrededor de 10 mg/l*", después de haber constatado que el 35% de los laboratorios participantes en un estudio en Gran Bretaña no eran capaces de detectar una BJP de 60 mg/l (6 mg/dl) (*Detection of Bence Jones Protein in Practice. R. Beetham - Ann Clin Biochem 2000; 37: 563-570*).

En la orina de pacientes normales las BJP en particular deben estar ausentes y, de una manera más general sólo deben haber trazas de la presencia de CLL policlonales. En consecuencia, cualquier valor detectable de CLL debería ser considerado potencialmente positivo y debería confirmarse su distribución (monoclonal o no) con una Inmunofijación, al objeto de descartar la presencia de BJP.

De todos modos, ni está establecido ni hay acuerdo sobre el significado clínico de pequeñas cantidades de BJP y, además, la sensibilidad del método nefelométrico se ha mostrado en algunos estudios superior a la de la Inmunofijación empleada como confirmación. Así pues, aunque la elección más purista sería usar como valor discriminante el límite de sensibilidad de la metodología nefelométrica, en la práctica la mayoría de usuarios emplean el valor propuesto de 5 mg/l (punto bajo de la curva de calibración) o muchos incluso 10 mg/l, tal y como detalla la poca bibliografía disponible, como valor discriminante para el cribado.

Nota (*3) - Antisueros Empleados en la Inmunofijación :

El esquema clásico, tipo suero, usualmente empleado prevé el uso de los siguientes antisueros: IgA, IgG, IgM, Cadenas Kappa (libres+ligadas) y Cadenas Lambda (libres+ligadas). El empleo de este esquema en la orina puede presentar complicaciones interpretativas que pueden dar lugar a resultados falsamente negativos para la presencia de BJP, como por ejemplo en aquellos casos en que la presencia de una Inmunoglobulina completa monoclonal enmascare la banda de BJP debido a una comigración aparente (situación que se supone poco frecuente, porque usualmente no se controla, pero que en la práctica se da con una frecuencia significativa).

Para la orina resulta más seguro y por lo tanto recomendable emplear el esquema alternativo que prevé el uso de antisueros anti Cadenas Ligeras Libres: Polivalente IG's, Cadenas Kappa (libres+ligadas), Cadenas Lambda (libres+ligadas), Cadenas Kappa Libres y Cadenas Lambda Libres.

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Relación Bibliográfica - Abstracts :

9. Clinical applications of immunoglobulin free light chain estimations

Int J Clin Lab Res 1993;23(1):25-9 (ISSN: 0940-5437)

Tillyer CR

Department of Chemical Pathology, Royal Marsden Hospital, London, UK.

The relevance of free light chain assays to diagnosis, staging, treatment and prognosis assessment in B-cell disorders (including myeloma, chronic lymphocytic leukaemia, and lymphoma), multiple sclerosis and diabetes is discussed and their actual and potential use is examined.

10. BUN, Bence Jones protein, and chromosomal aberrations predict survival in multiple myeloma

Rinsho Ketsueki 1997 Dec;38(12):1254-62 (ISSN: 0485-1439)

Okada K; Oguchi N; Shinohara K; Tamura N; Ishii K; Noguchi Y; Hayashi S; Yamamoto H; Takeichi M; Fujimoto H; Shirota T; Hayashi T

Third Department of Internal Medicine, Tokyo Medical College.

The prognostic significance of some clinical features in 41 patients with multiple myeloma (including 2 patients with plasma cell leukemia) from our institution was analyzed. Out of 14 variables isolated from the univariate analysis ($P < 0.05$), only three (BUN, Bence Jones protein, and chromosomal aberrations) were significant in the multivariate model ($P < 0.05$). Derived from these three variables, three subpopulations of patients were identified. The first group included 20 patients with a low risk of death and their median survival has not been reached. In particular, no one died during the first 60 months in this group. The second group also included 14 patients with an intermediate risk of death and a median survival of 49.2 months. The third group comprised seven patients with a high risk of death during 24 months after diagnosis and a median survival of 31.6 months ($P < 0.0001$). Finally, Durie & Salmon's myeloma staging system was demonstrated in the present series, and it showed prognostic validity for each stage ($P < 0.0222$). Compared with Durie & Salmon's staging system, our prognostic model for multiple myeloma was more useful to predict prognosis when applied to the present series.

11. Monoclonal free light chains in urine and their significance in clinical diagnostics: are they really tumor markers?

J Clin Lab Anal 1990;4(6):443-8 (ISSN: 0887-8013)

Vegh Z; Otto S; Eckhardt S

National Institute of Oncology, Budapest, Hungary.

Bence Jones proteins (monoclonal free light chains of immunoglobulins) are the earliest known biological markers of malignant cell dyscrasia; Bence Jones proteinuria is also present in many types of B cell-related neoplasms. Sometimes, it may also occur in Hodgkin's disease. In some cases, benign monoclonal gammopathy was found to be associated nontumorous diseases as well. The type of monoclonal light chain, the degree of polymerization, and the isoelectric point of the molecule may affect the course of the disease. Urine samples from 637 patients with true or suspected lymphoproliferative diseases were investigated over a 2-yr period by different immunochemical methods. Bence Jones proteinuria was identified in 71 cases by isoelectric focusing combined with immunofixation, while the pathological protein was detected only in 63 cases by conventional methods. Bence Jones proteins can be detected by this new method at a level below the sensitivity of conventional procedures. Bence Jones proteins in the urine may signal a malignant tumor or malignant transformation of an earlier disease. The early detection of monoclonal immunoglobulin light chains in the urine may be important in clinical diagnosis, therapy, and follow-up.

12. Antitumor activity of thalidomide in refractory multiple myeloma

N Engl J Med 1999 Nov 18;341(21):1565-71 (ISSN: 0028-4793)

Singhal S; Mehta J; Desikan R; Ayers D; Roberson P; Eddlemon P; Munshi N; Anaissie E; Wilson C; Dhodapkar M; Zeddis J; Barlogie B

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BACKGROUND: Patients with myeloma who relapse after high-dose chemotherapy have few therapeutic options. Since increased bone marrow vascularity imparts a poor prognosis in myeloma, we evaluated the efficacy of thalidomide, which has antiangiogenic properties, in patients with refractory disease.

METHODS: Eighty-four previously treated patients with refractory myeloma (76 with a relapse after high-dose chemotherapy) received oral thalidomide as a single agent for a median of 80 days (range, 2 to 465). The starting dose was 200 mg daily, and the dose was increased by 200 mg every two weeks until it reached 800 mg per day. Response was assessed on the basis of a reduction of the myeloma protein in serum or Bence Jones protein in urine that lasted for at least six weeks.

RESULTS: The serum or urine levels of paraprotein were reduced by at least 90 percent in eight patients (two had a complete remission), at least 75 percent in six patients, at least 50 percent in seven patients, and at least 25 percent in six patients, for a total rate of response of 32 percent. Reductions in the paraprotein levels were apparent within two months in 78 percent of the patients with a response and were associated with decreased numbers of plasma cells in bone marrow and increased hemoglobin levels. The microvascular density of bone marrow did not change significantly in patients with a response. At least one third of the patients had mild or moderate constipation, weakness or fatigue, or somnolence. More severe adverse effects were infrequent (occurring in less than 10 percent of patients), and hematologic effects were rare. As of the most recent follow-up, 36 patients had died (30 with no response and 6 with a response). After 12 months of follow-up, Kaplan-Meier estimates of the mean (+/-SE) rates of event-free survival and overall survival for all patients were 22+/-5 percent and 58+/-5 percent, respectively.

CONCLUSIONS: Thalidomide is active against advanced myeloma. It can induce marked and durable responses in some patients with multiple myeloma, including those who relapse after high-dose chemotherapy.

21. Renal insufficiency due to light chain multiple myeloma

Ned Tijdschr Geneeskd 2000 Nov 4;144(45):2133-7 (ISSN: 0028-2162)

van Zaanen HC; Diderich PP; Pegels JG; Ruizeveld de Winter JA

Sint Franciscus Gasthuis, afd. Inwendige Geneeskunde, Rotterdam.

In 3 female patients, aged 65, 83 and 76 years, with severe renal failure, light chain multiple myeloma was diagnosed, following a substantial delay on the part of the doctors concerned. Either the diagnosis had not suspected or the serum proteins had been misinterpreted. After a while, the first two patients declined further treatment with chemotherapy and haemodialysis, and subsequently died. The third patient attained a creatinine clearance of 20 ml/min and was subsequently treated for the multiple myeloma in the outpatients department. The absence of a paraprotein peak in the serum does not exclude the possibility of a multiple myeloma. In the case of light chain disease, the gammaglobulin region is, in fact, often empty. Treatment of multiple myeloma consists of a rapid rehydration and forced diuresis; the usefulness of plasmapheresis has not been demonstrated.

22. The kidney in multiple myeloma. The physiopathological and clinical aspects

Recenti Prog Med 1994 Feb;85(2):123-33 (ISSN: 0034-1193)

Vivaldi P; Comotti C; Pedrazzoli M

UO Medicina 2o, Istituto Ospedaliero S. Chiara, Trento.

The renal concern in a multiple myeloma (MM) case has a frequency of 50% and causes a worsening of the disease with a survival average of about 12 months. The monoclonal light free chains (CLL) produced in excess by the plasmacytes are present in the urine as proteinuria of Bence Jones (PBJ) in 60-70% of patients affected by MM. They represent the major pathogenetic factor of the nephropathy in course of MM as they can deposit in shape of intratubular "casts" in the myeloma casts nephropathy (MCN). In some worse cases, dehydration or hypercalcaemia can cause an irreversible acute renal insufficiency (RI). It is therefore important in a patient affected with MM with PBJ to prevent, locate and opportunely treat these situations which worsen the nephropathy. Beside the tubular cast nephropathy, the CLL "accumulate" in the kidney even though with a lower frequency compared to MCN, in the light chains deposition disease (LCDD) and in the amyloidosis AL (AL). LCDD is characterized by a deposit of nodular amorphous materials PAS positive in the glomerulus and sometimes even in the tubulus. It usually presents itself as a chronic RI and a proteinuria causing nephrotic syndrome (NS). This quickly evolves into uraemia and its evolution can be lessened by the MM treatment. AL in course of MM also reeals with a chronic RI and NS. CLLs deposit in the typical fibrillar structure, on the vessel walls, in the glomerulus, in the mesangium and can be marked out with the Congo red colouring and the subsequent green birefringence through microscope with polarized light. Prognosis of AL is extremely severe and no benefit is given by the treatment of the hematological illness. It is therefore absolutely necessary to study the renal histology through biopsy when MM is grade B, that is, with serumal creatinine above 2 mg/dl as: MCN imposes the MM treatment programme in order to reduce the tubular excess of PBJ and to attempt to make RI reversible; MCN with tubular atrophy and interstitial fibrosis results in an unfavourable prognosis as it expresses a nephropathic irreversibility due to the loss nephrons. It will therefore necessary to start on a renal substitutional treatment programme. Renal damage in course of MM is not always tubular, rather an unexpected glomerular damage of LCDD or amyloidosis AL type can be found.(ABSTRACT TRUNCATED AT 400 WORDS).

23. Immunoturbidimetric assay for estimating free light chains of immunoglobulins in urine and serum.

J Clin Pathol 1991 Jun;44(6):466-71 (ISSN: 0021-9746)

Tillyer CR; Iqbal J; Raymond J; Gore M; McIlwain TJ

Department of Chemical Pathology, Royal Marsden Hospital, Sutton, Surrey.

An immunoturbidimetric assay for the assessment of free kappa and lambda light chains of immunoglobulins was developed using a commercial polyclonal antiserum with reactivity towards epitopes on the light chains, which are not expressed when they are bound to heavy chains. The assay, on a centrifugal analyser, is simple and rapid. The limit of detection is 5 mg/l of free light chain, with an assay range of 5-120 mg/l, intrabatch precisions from 1.5-6.4%, and interbatch precisions from 6.5-8.9%. The assay was only slightly less sensitive than colloidal gold staining of cellulose acetate electrophoreses for the detection of Bence-Jones protein in urine. For the serial monitoring of response to chemotherapy in patients with myeloma, the assay correlated well with serum paraprotein estimates obtained by densitometric scanning of Ponceau stained cellulose acetate electrophoreses, but not with serum beta-2 microglobulin measurements, even after correction for the effects of creatinine. These assays may prove to be of use for the monitoring of tumour response in the treatment of Bence-Jones myeloma.

24. Clinical applications of immunoglobulin free light chain analysis

Int J Clin Lab Res 1994;24(2):120-1 (ISSN: 0940-5437)

Pascali E

The potential of immunoglobulin-free light chain detection and measurement in biological fluids, and particularly in urine, has not yet been fully explored in clinical medicine, because of differences in sensitivity and lack of standardization of both quantitative assays and qualitative analysis. The ability to identify monoclonal free light chain, i.e., Bence-Jones protein, reliably in urine is of great clinical interest even when it occurs only in such small amounts that they frequently remain undetected by the routine methods used in many laboratories. The standardized adoption of both qualitative and quantitative procedures with comparable sensitivity is suggested to allow precise characterization of the clonal nature, and therefore the clinical role, of any free light chain excess.