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Free Light Chains Nephelometric Assay: Great Versatility

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Immunoglobulin light chains that are circulating in serum in a free state are called Free Light Chains (FLCs). FLCs are secreted by plasma cells and can be found in body fluids such as blood, synovial and cerebrospinal fluid, urine, and saliva [1].

The production of FLCs in normal individuals is approximately 500 mg/day from bone marrow and lymph node cells and they have a serum half-life of 2–6 h. When FLCs are produced in excess, the reabsorptive capacity of the tubules can be overwhelmed, thus leading to an accumulation of FLCs in the serum [2, 3].

FLCs are an important diagnostic marker for monoclonal gammopathy and, for more than 150 years, the presence of Bence Jones protein in the urine has been the key indicator of immunoglobulins production. Monoclonal proteins are typically detected by serum protein electrophoresis (SPE) and immunofixation electrophoresis (IFE). Indeed diseases like amyloidosis L (AL) light chain multiple myeloma (LCMM), light chain deposition disease (LCDD) and smolderingmieloma (SMM) often do not have enough concentrations of serum monoclonal proteins to be detected and quantified by SPE.

During the last decade, there has been a paradigm shift with the availability of automated immunoassays that independently measure kappa (κ) and lambda (λ) FLCs in the serum with a higher sensitivity of the SPE.

Laboratory methods to screen for monoclonal gammopathies historically comprise SPE and urine protein electrophoresis (UPE). Monoclonal proteins (M-proteins) migrate as discrete bands on an electrophoretic gel, appearing as a densitometric peak, which provides a semi-quantitative value for the amount of M-protein. After the identification of an M-protein by SPE, the serum IFE is required for confirmation of clonality and subsequent typing. Actually, the International Federation of Clinical Chemistry (IFCC) Guidelines recommend SPE and IFE in serum and urine for the diagnosis and monitoring of multiple myeloma (MM) and of similar diseases[4].

IFE is also recommend to detect intrathecal immunoglobulin synthesis [5] but the test has not been incorporated into diagnostic use for multiple sclerosis (MS). The FLCs concentration has been technically difficult in the past and not feasible in routine clinical diagnostics [6].

Currently, the most commonly used methods for FLCs (κ and λ) determination are nephelometric and turbidimetric techniques which use a specific antibody to recognize the hidden antigenic determinant of LCs (usually covered by heavy chains in the intact Ig molecule) to avoid falsely elevated FLC from cross-reaction.

These automated assays are reported to be more sensitive than IFE for detection of monoclonal FLCs and could change the determination of BJ proteinuria (BJP)and intrathecal synthesis in cerebrospinal fluid (CSF).

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FLCs in Urine Sample

The determination of BJP is essential when clinical suspicion of MG persists and serum tests are negative; moreover it is useful to perform the diagnosis of MG [7, 8] and to monitor response to therapy in MM. Urine FLCs concentration can probably still be useful for begin therapy and as support to highlight burden in patients with MM and related disorders [9, 10]. There is interest in Minimal Residual Disease (MRD) monitoring, that can be used as a prognostic factor and to predict patients' outcomes in MM [11]. In a precedent study we compare the performance of the nephelometric assays to IFE agarose gel in urine samples to assess the correlation between the results of two tests and the clinical diagnosis (negative or positive for B cell proliferative disorders) [12]. In our study, 10% of the samples showed discordance between IFE and nephelometric assay. By analyzing these results to clinical diagnosis, the nephelometric dosage showed a correlation of 92% while gel assay only of 8%. In our opinion, the discordant cases may be due to the subjectivity in reporting gel: in fact, the presence of a slight band in the gel (not a numerical data) can affect those who validate while nephelometric assay is quantitative, rapid and not operator depending. These data suggest that urine FLCs nephelometric dosage may represent an important marker for the evaluation of the MRD, for early detection of the biochemical relapse, for therapy monitoring and follow up.

FLCs in CSF sample

Intrathecal immunoglobulin synthesis is commonly observed in inflammatory disorders of the central nervous system (CNS) of either infectious or autoimmune origin [13, 14]. It is necessary to differentiate the origin of Ig in the CSF before intrathecal synthesis can be diagnosed [15]. This can be achieved either by calculation of the CSF/serum ratios of immunoglobulins compared with the CSF/serum ratio of albumin (Qalb), which is not synthesized intrathecally, or by the detection of so-called oligoclonal immunoglobulin bands

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(OCBs) in CSF [16, 17]. In general, the analysis of OCBs is time-consuming, not quantitative, and subject to investigator bias [13, 16]. The nephelometric determination of free light chains (FLCs) might be a sensitive alternative to the above-mentioned approaches [18-21]. Many studies have shown the correlation between OCBs test and the nephelometric assay, highlighting the greater sensitivity and specificity of the latter in the detection of intrathecal immunoglobulin synthesis [14, 21, 22]. Analyzing the FLCs concentration, in particular k chains, we observed that the kFLC Index provides a specific means to follow intrathecal immunoglobulin synthesis and seems to be more accurate especially in patient with impaired CSF-serum barrier [14]. Furthermore kFLCs Index, having a best sensitivity and specificity in the diagnosis of MS, could replace the OCBs test and help the neurologists to monitor the progress of the patient's treatment.

In conclusion, the nephelometric determination of FLCs in serum, urine and CSF is a quantitative specific method, sensitive, non-operator dependent, rapid and therefore could be included in routine analysis.

Competing Interests

The Authors declare that they do not have any competing interest.

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