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SERUM FREE LIGHT CHAIN TESTING FOR PARAPROTEIN IDENTIFICATION INFORMATION SHEET

INTRODUCTION

Immunoglobulin heavy and light chains are expressed separately by plasma cells and B lymphocytes, where they are assembled into immunoglobulin molecules of the different heavy and light chain isotypes. Free Kappa (K) and Lambda (L) light chains are normally produced in excess of heavy chains. These normal excess free light chains are secreted from plasma cells/B lymphocytes as monomers, dimers and occasionally multimers, with their serum levels being determined by the balance between their production and degradation. With normal renal function the greatest degradation occurs in the renal tubules and to a lesser extent by the mononuclear phagocyte system. K free light chains are produced in excess of free L but their renal clearance is much faster.

SFLC ASSAYS

Free K and L chains are measured separately using polyclonal antibodies to light chain epitopes which are only visible to the immune system when they are unbound (free) of immunoglobulin heavy chains. The results are presented as the level of free K, free L and the K/L ratio.

Reference range for free K 3.3-19.4 mg/L

Reference range for free L 5.71-26.3 mg/L

Reference range K/L ratio 0.26-1.65

With renal dysfunction normal K/L ratio changes progressively from normal to 0.37 - 3.10.

INDICATIONS FOR ORDERING SFLC ASSAY

Monoclonal proliferation of B cells or plasma cells, occurs in conditions such the various forms of multiple myeloma, plasmacytoma, monoclonal gammopathy of uncertain aetiology (MGUS), Waldenstrom's macroglobulinaemia, primary amyloid, POEMS syndrome and light chain deposition disease. This results in an unbalanced production of either free K or L chains which can be detected as an elevation of either free K or free L chain levels and a skewing of the normal K/L ratio.

The SFLC assay can therefore be ordered alone to help identify the presence of a monoclonal paraprotein, which it does with a sensitivity of about 74%, compared to a sensitivity of about 87% for serum electrophoresis (EPG)/immunofixation. The combination of serum and urine EPG/immunofixation or SFLC and serum EPG/immunofixation each identifies about 97% of monoclonal paraproteins. A combination of SFLC, serum and urine

EPG and immunofixation is said to detect about 99% of patients with serum paraproteins or urine free light chains (Bence Jones protein).

The sensitivity of the SFLC assay, in most circumstances allows this assay to be used to identify patients with only urine free light chains. Whilst this approach will miss a small proportion of such patients, these are mainly those with more benign disorders such as monoclonal gammopathy of uncertain significance (MGUS). The sensitivity of this assay means that it has a particular value in conditions where very little paraprotein is produced (e.g. non-secretory myeloma) or where only free light chains are produced (e.g. light chain myeloma and amyloid)

SFLC assays cannot determine the heavy chain isotype of a paraprotein and cannot determine if light chain production is such that free light chains (Bence Jones Protein) spill over into urine. Because of this and confounding factors, discussed below, in most circumstance SFLC assay should be ordered as part of one of the test panels suggested above.

CONFOUNDING FACTORS

Renal clearance is a major mechanism for degradation of free light chains that disproportionately impacts free kappa compared to free lambda. Renal disfunction therefore effects interpretation of this assay with the normal K/L ratio changing progressively from normal (0.26-1.65) to 0.37 - 3.10 (renal reference range).

Uncommonly, technical factors can affect the performance of SFLC assays. Antigen excess associated with very large paraproteins may rarely cause falsely low levels of the relevant light chain. Non-linearity with some samples, caused by interaction between some free light chains and other plasma proteins, can cause completely different results with different dilutions of the patient sample. Both can uncommonly cause erroneous or misleading results.

SFLC assay may be insensitive to bi-clonal paraproteins of different light chain isotype (e.g IgGK and IgGL or IgAL and IgGK. For example, the K paraprotein may balance the L paraprotein leading to a normal K/L ratio. Alternatively, the dominant paraprotein may outweigh the lesser one leading to the identification of only one paraprotein rather than two paraproteins.

The limitations of the SFLC assay can be minimised by ordering multiple different assays to detect paraproteins, as suggested above.