All Wales Clinical Biochemistry Audit Group

Standards for the Investigation of Serum and Urine Paraproteins

INTRODUCTION

A survey of methods used by laboratories in Wales for paraprotein investigations was carried out in July 1994 by the late Dr.R.Fifield and presented by him at an audit meeting in January 1995. The survey showed that most laboratories were adhering to recommendations for best practice,[1] which were presented at the meeting and are outlined below, with some modifications.

STANDARDS

1. Investigation of Serum Paraproteins

a) Serum protein electrophoresis, preferably performed on agarose gel, is recommended as the first step to identify the presence of a monoclonal band.

b) Immunofixation is preferred to immunoelectrophoresis as the method for typing paraproteins. Immunochemical evaluation by measurements of κ, λ, IgA, IgG and IgM concentrations can type up to 95% of serum paraproteins detected by an abnormal κ/λ ratio,[2] although selective immunofixation is recommended to confirm the paraprotein type, and full immunofixation is required to categorise the remainder.

c) Referral to a specialist laboratory (such as a Protein Reference Unit) is recommended if the presence of an IgD or IgE paraprotein is suspected.

d) Scanning densitometry of the electrophoretic strip, related to the serum total protein concentration, is recommended for quantitation of the serum paraprotein concentration. Immunochemical assays may overestimate serum paraprotein concentrations[3] and should only be used to measure concentrations of non-monoclonal immunoglobulins, e.g. only IgA and IgM if the paraprotein is IgG, primarily to seek evidence of immunoparesis.

e) Measurement of serum ß2-microglobulin is recommended at presentation as an indicator of prognosis.

2. Investigation of Urine Paraproteins

a) Urine as well as serum should be analysed if a paraprotein is suspected.

b) It is recommended that the analytical technique used should have a detection limit of ≤ 10 mg/l for Bence-Jones protein.

c) Recommended methods for the identification of urine paraproteins are:
   (i) Protein electrophoresis followed by immunofixation;
   (ii) Immunoblotting.

d) Protein electrophoresis is preferably done on agarose gel. Prior urine concentration (according to the total protein value) is generally required, but has disadvantages and is not essential with some commercial kits or sensitive stains (e.g. colloidal gold).

e) Immunofixation is recommended if band(s) other than albumin are seen on electrophoresis and is preferred to immunoelectrophoresis for typing paraproteins

f) The value of urine paraprotein quantitation is debatable; if performed, the preferred method is densitometry of the electrophoretic strip, related to the urine total protein concentration.

3. Quality Issues

a) It is recommended that all laboratories undertaking paraprotein quantitation should assay an internal quality control sample containing a paraprotein of known concentration in parallel.

b) It is recommended that all laboratories undertaking serum/urine paraprotein typing and/or serum paraprotein quantitation should participate in a suitable EQA scheme, such as the UK NEQAS for monoclonal paraproteins (currently based in Sheffield).

c) It is recommended that the turn-round time for paraprotein investigations should not usually exceed 1 week.

d) Effective communication with clinical staff is important in investigating and managing patients with paraproteins. It is recommended that the discovery of a new paraprotein is formally communicated to the requesting clinician and also to the local haematologist or oncologist responsible for the clinical management of patients with multiple myeloma and related disorders.

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REFERENCES

1. Whicher JT, Calvin J, Riches P, Warren C. The laboratory investigation of paraproteinaemia. Ann Clin Biochem 1987; **24**: 119-132.
2. Fifield R, Keller I. An immunochemical evaluation for the identification and typing of monoclonal proteins. Ann Clin Biochem 1990; **27**: 327-334.
3. Riches PG, Sheldon J, Smith AM, Hobbs JR. Overestimation of monoclonal immunoglobulin by immunochemical methods. Ann Clin Biochem 1991; **28**: 253-259.
4. Beetham R. Detection of Bence-Jones protein in practice. Ann Clin Biochem 2000; **37**: 563-570.

VERSION: 1a

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Appendix

CALENDAR of Audit Process for Standards for Investigation of Serum and Urine Paraproteins

July 1994	Survey of all 13 Welsh clinical biochemistry laboratories which perform paraprotein investigations undertaken by Dr.R.Fifield (late Consultant Biochemist, Cardiff Royal Infirmary).
January 1995	Findings of survey presented by Dr.R.Fifield at an All Wales Clinical Biochemistry Audit Group meeting at Nevill Hall Hospital, Abergavenny and recommendations for best practice proposed by him.
January 2000	In response to a letter from Dr.M.Penney (Consultant Chemical Pathologist, Royal Gwent Hospital, Newport), the All Wales Clinical Biochemistry Audit Group committee agreed to arrange for draft standards to be written based on the recommendations for best practice proposed by Dr.Fifield.
March 2000	Draft standards prepared by Dr.D.Oleesky (Medical Biochemist, University Hospital of Wales) following Dr.Fifield's death and sent for consultation to consultant biochemists in Wales and also to Professor A.K.Burnett (Professor of Haematology, University of Wales College of Medicine) to seek the views of haematologists in Wales.
October 2000	Draft standards presented by Dr.D.Oleesky at an All Wales Clinical Biochemistry Audit Group meeting at the Royal Glamorgan Hospital, Llantrisant and discussed. This meeting was also attended by Professor Burnett and by experts in protein immunochemistry from England.
Nov. 2000	Standards amended, finalised and ratified at an All Wales Clinical Biochemistry Audit Group committee meeting (on 22nd November 2000) by Dr.K.Griffiths (chairman).
January 2005	Standard 1a modified, as use of κ/λ ratio as the initial screening test is no longer considered best practice.
2006	Proposed date of re-audit.