Review

Cerebrospinal fluid protein and glucose examinations and tuberculosis: Will laboratory safety regulations force a change of practice?

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Abstract
Cerebrospinal fluid (CSF) protein and glucose examinations are usually performed in chemical pathology departments on autoanalysers. Tuberculosis (TB) is a group 3 biological agent under Directive 2000/54/EC of the European Parliament but in the biochemistry laboratory, no extra precautions are taken in its analysis in possible TB cases. The issue of laboratory practice and safety in the biochemical analyses of CSF specimens, when tuberculosis infection is in question is addressed in the context of ambiguity in the implementation of current national and international health and safety regulations. Additional protective measures for laboratory staff during the analysis of CSF TB samples should force a change in current laboratory practice and become a regulatory issue under ISO 15189. Annual Mantoux skin test or an interferon-γ release assay for TB should be mandatory for relevant staff. This manuscript addresses the issue of biochemistry laboratory practice and safety in the biochemical analyses of CSF specimens when tuberculosis infection is in question in the context of the ambiguity of statutory health and safety regulations.

Key words: glucose; proteins; cerebrospinal fluid; tuberculosis; safety; accreditation

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Introduction
Cerebrospinal fluid (CSF) protein and glucose examinations in confirmed and possible cases of tuberculosis (TB) are carried out in the chemical pathology laboratory. CSF protein is normally derived from plasma and protein levels are < 1% of plasma levels (1). CSF glucose is normally about 60% of plasma levels. The normal CSF/plasma glucose ratio varies from 0.3 to 0.9 with variation in CSF glucose in response to changes in blood glucose reflecting a lag phase in CSF/blood equilibrium time. During the recovery phase in the treatment of meningitis, CSF glucose normalizes before protein levels and cell counts. Patients with chronic tuberculous meningitis have abnormal CSF with lymphocytic pleocytosis, decreased glucose and increased protein (2). In routine practice, CSF biochemical analyses in meningitis may include lactate, C-reactive protein, adenosine deaminase and lactate dehydrogenase.

This manuscript addresses the issue of biochemistry laboratory practice and safety in the biochemical analyses of CSF specimens when tuberculosis infection is in question in the context of the ambiguity of statutory health and safety regulations. The Health and Safety Authority in Ireland has formally challenged the safety of current laboratory practice in the biochemical analysis of CSF samples where group 3 biological agents are concerned and the issue has implications across the European Union. A “group 3 biological agent” may cause severe human disease and represents a serious hazard to employees thus presenting a risk of spreading to the community, although there is usually effective prophylaxis or treatment availa-
Tuberculosis, laboratory health and safety and regulation

Tuberculosis is a group 3 biological agent as listed in Code of Practice for the Safety, Health and Welfare at Work (Biological Agent) Regulations 2013 in Ireland. These Regulations transpose Directive 2000/54/EC of the European Parliament. Containment restrictions are required by the regulations. Regulation 3 (1) states: “these Regulations and any relevant code of practice, apply to activities in a place of work where existing or potential, whether deliberate or incidental, exposure to a biological agent has occurred or may occur” (3).

Schedule 2 of the Safety Health and Welfare (Biological Agents) regulations lists the measures for prevention and risk reduction. There is a requirement to design work processes and engineering control measures to avoid or minimize the risk of the release of a biological agent into the place of work. Hygiene measures must be used to prevent or reduce accidental transfer or release of a biological agent from the place of work. Collective and individual protective measures must be used where exposure cannot be avoided by other means. A further requirement is unclear and states that “the testing, where necessary and technically possible, for the presence, outside the primary physical confinement, of a biological agent used at work” (4). In the context of TB, the requirements seem to require special suited protection, a negative air pressure safety cabinet and a separate area for TB biochemical testing.

Are these requirements current practice in general hospital laboratories? From enquiries in Ireland and the UK, the answer appears to be No!

Conventional practice

There are no special precautions with regard to biochemistry sample analysis and infectivity listed or referred to in Henry’s textbook with regard to cases where TB is a differential in the diagnosis (1). The TB reference laboratory in Ireland does not recommend any particular laboratory precautions such as negative pressure fume cupboards and full masks and gowns. Neither do the Canadian, UK or Indian or United States Guidelines (5-8).

Lack of evidence of laboratory staff infection

In a survey of laboratory staff in the UK, two cases of TB were reported in a biochemistry department within 18,310 person years of exposure. Details were not provided (9). While there is a theoretic risk, it must be witheringly small. In contrast, the risk to nurses even in short contact with an infectious patient is real. In 2012, there were 364 cases of tuberculosis reported in Ireland of which 3 (0.8%) were TB meningitis.

The literature on laboratory associated infections reveals 5,346 such infections between 1930 and 2000. These cases appear to refer to microbiology processes overwhelmingly. Historic data from the United States in the period from 1930 to 1950 found a total of 775 cases of laboratory-acquired infections of which 153 were TB. World data from 1950 to 1963 revealed 191 cases of which 21 were TB. In a literature survey covering 1979–2004, there were 1,141 laboratory acquired infections of which 199 were Mycobacterium tuberculosis (10). Data from England and Wales found that laboratory workers showed a 5.4 times increased risk of acquiring TB compared to the general population with the highest risk ratio 7.5 among technical staff.

Surveillance precautions

The US Morbidity and Mortality Weekly Report issued guidelines on the prevention of transmission of TB in healthcare settings in 2005. Laboratory workers should be screened for TB if they share airspace with an infected person or if they participate in suspected or confirmed TB specimen processing. As a surveillance precaution, all health care workers should have baseline TB screening.
on job commencement using a two-step tuberculin skin test or a single whole blood gamma interferon assay. Annual clinical appraisals should then be carried out. Medical scientists may need respiratory protection depending on the type of ventilation in use in the laboratory and the likelihood of aerosolization of viable TB as a result of a laboratory procedure (11).

**Codes of practice**

In the US, Biosafety in Microbiological and Biomedical Laboratories (BMBL) has become the code of practice for biosafety (12). No reference is made to processing CSF specimens in a biochemistry autoanalyzer but any maneuver that produces an aerosol heightens the infection risk. The requirement for tuberculosis is that "all aerosol-generating activities must be conducted in a biological safety cabinet". Biosafety Level 2 (BSL-2) practices and procedures seems the safest protocol to adopt but in practice, how will this be applied to biochemical analyses of CSF samples? The availability of simple, easy to use, point-of-care testing devices allow the routine use of biological safety cabinets for CSF glucose analysis but low levels of protein are beyond the device sensitivities. In England, TB is in hazard Group 3 and must be processed in a microbiological safety cabinet under full containment level 3 conditions. Does this happen with biochemical analyses in English or Irish hospitals? No!

A detailed public health report from Belgium in 2006, described common laboratory methodologies involved in TB analysis but biochemical autoanalysers did not feature (13).

**Current analytical practice**

The Beckman Coulter AU 5400 autoanalyser (Bath, UK) is used for estimation of CSF glucose and protein in this institution. Aerosol micro-droplets are possible in the process of autopipetting a specimen aliquot into the cuvette and also at the reagent mixing stage. All infectious blood specimens involving HIV, HepB, HepC and unknown are treated in a similar manner. It is impossible to eliminate all risk from infectious pathogens.

**Accreditation challenge and improved safety monitoring**

ISO 15189 accreditation inspectors have not focused or commented on this issue to date. Will the precautionary principle be applied with CSF glucose and protein analysis being performed in negative pressure cabinets with staff in space suits using specially designated equipment or will common sense prevail and current practice continue?

It is possible that additional preventive measures for biochemical analyses of TB specimens will become the norm because health and safety regulations specify more stringent precautions than are currently in widespread practice. Where suitably sensitive point-of-care devices for relevant biochemical analytes become available, these can be used in the negative air pressure biological safety cabinets in the microbiology departments which would divert the issue away from biochemistry technologists.

**Concluding recommendation for staff**

Staff involved in testing of TB specimens in clinical chemistry laboratories as well as those in microbiology laboratories should have baseline screening for TB on job commencement and follow-up annual clinical appraisals. Annual Mantoux skin test or an interferon-γ release assay should be done to check for conversion. Those with positive results should have a chest X-ray and appropriate treatment. These annual staff tests are not done in Clinical Chemistry departments at present.

**Potential conflict of interest**

None declared.
References


