The Alzheimer's Association QC program for CSF biomarkers

BACKGROUND

The CSF biomarkers tau and amyloid β (Aβ) show promise as tools in the diagnostic work-up patients with suspected Alzheimer's disease (AD) and to monitor treatment effects in AD clinical trials. However, recent multi-center studies have shown that the levels of these CSF biomarkers vary between different research centers and laboratories. This variation in CSF biomarker levels between laboratories complicates multicenter research studies and clinical trials, and also precludes the introduction of general cut-off levels.

The aim of the ongoing CSF QC program is thus to serve as a tool for efforts to standardize CSF biomarker measurements between both research and clinical laboratories. The program is run by the Clinical Neurochemistry Laboratory in Gothenburg, Sweden in conjunction with the Alzheimer's Association.

Biotech companies and a number of reference laboratories, including the Alzheimer's Disease Neuroimaging Initiative Biomarker Core, are also represented. Both research and clinical CSF laboratories, as well as pharmaceutical companies, are enrolled in the program. The program is open for generally (commercially) available assay formats, but not for in-house assays, and consists of two parts.

OUTLINE

In the QC program, CSF samples (aliquots of pooled CSF) are sent out to the participating laboratories for CSF biomarker analysis, after which biomarkers levels are entered into a report form and returned. The final report for each quality control round includes information on the measured biomarker levels for the individual laboratory and, for comparison, the mean and variation in biomarker levels across all laboratories involved in the program. In addition, the longitudinal stability in CSF biomarker levels for the individual laboratory, expressed as percent deviation over time, is reported. These reports will serve as feedback for the participating laboratories, to identify whether the level of a biomarker is outside an acceptable range and to note sudden changes or longitudinal drifts in CSF biomarker levels.

EXTENSION PROJECTS WITHIN THE QC PROGRAM

Initial results in the QC program verify a large variability between participating laboratories. This means that much work is needed on standardization of the three potential causes of variation. These include pre-analytical factors (e.g. lumbar puncture procedure and CSF sample processing), analytical (laboratory) procedures, and assay-related factors, especially batch-to-batch variation for the assays. For this reason, a number of extension projects are needed.

1) A standardized protocol for lumbar puncture (LP) and CSF sample processing

This flow chart on procedures for lumbar puncture and CSF sample processing gives recommendations on details for the LP and how to process a CSF sample in the laboratory. This protocol has also been published: Blennow, K. et al. Nat. Rev. Neurol. 6, 131–144 (2010).

2) Standardization of laboratory procedures

To reduce possible variance due to different techniques in how to run immunoassays between laboratories, recommendations that can be generally accepted are necessary. This project has been initiated, and a first draft for such recommendations will be made available for members in the QC program, for suggestions, comments, and final acceptance.

A checklist for the laboratory procedures will also be included in each round in the QC program. This checklist is to be filled in by the participating labs, to verify uniform (or identify differences in) laboratory procedures.

3) Improved assay batch-to-batch stability

A substantial part of the variability is most likely caused by assay-related factors, especially batch-to-batch variation in the production of assays. This involves a need for assay vendors to implement improved standards for quality control in the production of assays, so that kits will have low overall variability in calibration curves and strict limits of variability across batches. This has been initiated by the companies producing the assays.

4) The U GOT CSF samples

It is clear that much work is needed on standardization of all of pre-analytical and laboratory procedures and also on assay optimization, before we can see an acceptable variability between the participating laboratories in the QC program. The aim of the University of Gothenburg (U GOT) CSF project is therefore to provide a unique set of QC samples (U GOT CSF 2010) for standardization between clinical research studies and clinical trials.

The U GOT CSF 2010 QC samples have a volume of 0.5 mL and come from a large CSF pool that has been analyzed multiple times to determine biomarker levels with high precision. For clinical research studies and clinical trials, laboratories can request aliquots from Gothenburg for analysis together with their study samples. Up to 4 QC samples can be ordered for a specific study, which can be analyzed on different plates during the analyses. Investigators may then either normalize their study according to the QC sample levels, or report QC sample levels in their publications. This information will facilitate comparisons of CSF levels between studies.

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