Laboratory Bulletin

Date: **March 23, 2012**

To: **Alberta Micronet, AHW Office of Chief Medical Officer of Health, AHS Medical Officers of Health, Infectious Diseases Specialists, Neurologists, and Laboratory Directors, Managers and Pathologists**

From: **Provincial Laboratory for Public Health (ProvLab)**

Re: **Notice on enhanced CSF testing for Creutzfeldt-Jakob Disease (CJD) at the National Microbiology Laboratory (NML)**

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Key Message:

Effective immediately, following a recent upgrade to reference services provided by the National Microbiology Laboratory (NML), Cerebro-Spinal Fluid (CSF) samples submitted for 14-3-3 protein assay, coordinated through ProvLab, will also be tested for tau protein levels and for S100B protein levels.

Background:

The laboratory diagnosis of Creutzfeldt-Jakob Disease (CJD) remains difficult. Currently no definitive laboratory test is available on CSF samples for the pre-mortem diagnosis of CJD. However, surrogate assays that detect proteins released from brain tissue into the CSF during CJD in its clinical stage have proven useful in modifying diagnostic probabilities, and especially for sporadic CJD.

The most widely used is the 14-3-3 protein assay; this protein family participates in the protein kinase signaling involved in neuronal migration. In carefully selected patient populations with relatively high pre-test probability of having sporadic CJD, the assay achieved a sensitivity of 80% to 90%, with a specificity of 90%. However because the 14-3-3 is released upon neuronal death, high levels are also seen in other conditions such as encephalitis, cerebral infarction and paraneoplastic disease. In more general populations the positive predictive value was considerably lower (although the negative predictive value was 98%).

Supplemental assays measuring levels of tau protein (a phosphoprotein that binds to axonal microtubules) and S100B protein (a calcium-binding protein expressed at high levels in a subtype of mature astrocyte) have been found to improve the performance of CJD surrogate testing. Since these proteins can also be released in other diseases causing brain tissue destruction, interpretation of the results must be done in conjunction with other clinical data, including imaging and markers of inflammation in the CSF.

Interpretative criteria remain to be refined. The assays are quantitative and the post-test probability of CJD is increased if higher concentrations of these proteins are detected. Studies performed at NML, using the criterion of maximum Youden index (Sensitivity + Specificity -1), estimate an optimal threshold of 976 pg/mL for the tau protein, and of 2.5 µg/L (2.5ng/mL) for the S100B protein.

For genetic human transmissible spongiform encephalopathies, these three assays have been found to have good sensitivities for CJD variants E200K and V210I. These assays are typically negative in Gerstmann-Sträussler-Scheinker syndrome and Fatal Familial Insomnia.

For variant CJD (vCJD) linked to Bovine Spongiform Encephalopathy, the 14-3-3 assay is less useful since only about 50% of vCJD cases have a detectable level of 14-3-3 in the CSF.

Reporting format:

Assay:	**Performed as:**	**Reported as:**
14-3-3 assay	Western Blot	Positive or Negative
Tau Protein assay	ELISA	Protein levels in pg/mL
S100B Protein assay	ELISA	Protein levels in ug/L (ng/mL)

Testing Requirements:

CJD testing ***requires*** prior approval by the Virologist on Call (VOC):

- Edmonton Site – Phone: 780-407-7121 (ask for Virologist-on-Call)
- Calgary Site – Phone: 403-944-1200 (ask for Virologist-on-Call)

CSF samples ***approved*** for testing:

- Must be clearly labeled as " ***CJD Precautions***"
- Samples from such patients are assumed to contain prions and are classified as Dangerous Goods (6.2, UN 3373, Biological Substances, category B) and WHMIS Hazardous Material (Class D.3 biohazardous infectious material), and must be handled and transported accordingly as per AHS policy

References:

- Diagnostic accuracy of cerebrospinal fluid protein markers for sporadic Creutzfeldt-Jakob disease in Canada: a 6-year prospective study. Coulthart MB et al, BMC Neurology 2011; 11: 133
- NML Guide to Services, CJD: http://www.nml-lnm.gc.ca/guide2/pathogen_engview.php?refdiagID=14

Inquiries and feedback may be directed to:

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This bulletin has been reviewed and approved by Dr. Marie Louie, Acting Medical Director, ProvLab