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Neurochemical dementia diagnostics - Interlaboratory variation of analysis, reference ranges and interpretations in the European CSF Survey of INSTAND

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Introduction: In the external quality assessment system for dementia marker analysis in Cerebrospinal fluid (EQAS) of INSTAND, Germany, participate 49 laboratories from nine European countries and USA. Stabilized CSF samples with physiologically relevant data pattern are distributed to allow, together with the numerical data, a reference range - related evaluation and a differential diagnostic interpretation of combined parameters (total Tau protein, hyperphosphorylated Tau protein and Amyloid-β-peptide Aβ42).

Results: The inter-laboratory variation for the three parameters from N=6 surveys are shown to be a problem of the analytical methods: A 10-fold variation between lower and upper concentrations of the values for Aβ42 (69-771 pg/ml) with up to 31% outliers or a 4-fold variation for Tau (315-1292 pg/ml) with 13-15% outliers needs urgent reaction of the supplier. Only pTau results with less then twofold variation (53-83 pg/ml, Table 1) and only 3-11% outliers corresponding to success quota of 89-97% were of acceptable performance. For the evaluation of these numerical data (normal /pathological/border line) the participants used own cut off values with a huge variation: Tau (150-540, median 450 pg/ml), pTau (35-85, median 61 pg/ml) and Aβ1-42 (205-600, median 500 pg/ml). These data represent the dilemma of this analytical approach as shown in the examples: In case of a sample with normal median values (e.g. Tau=381 pg/ml and Aβ=748 pg/ml) 45% of participants regarded the value as pathological with a stunning interpretation of the combined data of Tau and Aβ1-42: 29% of the participants found this data combination compatible with an Alzheimer's disease, definitely a false pathological result. 29% report this as a normal sample, and still 42% regard an integrating interpretation as not possible. In case of pathological values (921/66/508 pg/ml) 30% of participants evaluated Aβ1-42 data as normal, 30% as decreased and 40% as borderline. In spite of this ambivalence in reference range-related evaluation 74% of the participants regarded their results compatible with the diagnosis of AD.

Conclusion: Up to 31% outliers are a source of serious diagnostic errors. The unacceptable large variation of the reference ranges (cut off values) used in daily practice with false negative and false positive diagnostic interpretations question the practical relevance of statistically founded differences between different dementive diseases as reported in the literature. Improvement of the assay performance with reliable control material for interlaboratory compatibility and a knowledge based consensus about cut off values are the precondition to avoid the confusing interpretations of combined biomarker data. The calculation of mathematical formulas or ratios are not improving the discriminative sensitivity due to the error propagation in mathematical functions with uncoupled analytical data.

Biography

Hansotto Reiber had Diploma in Biochemistry from the University Tübingen during the year 1964-1970. From 1971-1974, he worked in the department of Physical Chemistry as Thesis (Theory of Enzyme Kinetics), Dep. of Prof. Dr. M. Eigen, Max-Planck-Institute of Biophysical Chemistry, Göttingen. He joined as a Research Fellow in the Department of Neurochemistry, Max Planck-Institute of Experimental Medicine, Göttingen in the year 1974. In 1978-2005, he became Head of Neurochemistry Laboratory, Dep of Neurology, University of Göttingen 1984 Habilitation for Neurochemistry. Since 1988, he is working as a Professor for Neurochemistry, University of Göttingen. From 1991 he started working as a supervisor and organizer of CSF survey. In 2006, he was awarded as a Guest Professor by El pleno de la academia de ciencias de Cuba. In 2011 he became a member of the board of INSTAND since 2012 he gave Lectures in the Brasilian Academy of Neurology, in Curitiba, Rio de Janeiro, Sao Paulo. He has 190 peer reviewed publications e.g., on CSF analysis in inflammatory diseases, tropical neurological diseases, pediatric neurological diseases and investigations of inflammatory diseases of the eye. He was also the editor and contributions to textbooks.

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