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Review

Consensus recommendations of the Italian Association for Neuroimmunology for immunochemical cerebrospinal fluid examination

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Abstract

In 2002–2003, the Italian Association for Neuroimmunology (AINI) ran a program for procedure and method standardization in neuroimmunology. The main purposes of the program were: a) to improve the overall quality of analytical performance and, simultaneously, to reduce costs by resource optimization; b) to establish the bases for clinical guidelines in neurology; c) to promote the formation of laboratory networks and of joint research projects; d) to facilitate the procedures for certification required by governmental/non-governmental agencies. This report summarizes the consensus recommendations of a panel of AINI neuroimmunologists/biochemists involved in the field of cerebrospinal fluid examination. The collection process for said recommendations was guided by "impact-factored" literature and the knowledge of the experts involved. Communication was by email and face-to-face at two dedicated AINI workshops.

Keywords: Cerebrospinal fluid; Diagnostics; Isoelectric focusing; Laboratory standardization; Multiple sclerosis; Neurological diseases; Oligoclonal bands

Contents

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1. Introduction

Cerebrospinal fluid (CSF) examination produces results in both the routine and the research fields, but procedures and methods are incompletely standardized. For instance, the number of oligoclonal IgG bands (OCBs) has been reported as being associated with multiple sclerosis (MS) prognosis [1], or as being able to discriminate between MS and other inflammatory/infectious neurological diseases [2]; however, such reports lack conviction without previous studies on between-laboratory reproducibility of the number of bands. Consequently, the reported clinical correlations with band numbering are not easily exportable. More generally, a lack of standardization is one of the causes of the lack of agreement between studies on CSF biomarkers. Another important cause is that these studies usually assess diagnostic performance of measuring tests in the best a priori experimental conditions (i.e., in selected populations of cases and controls), without any a posteriori evaluation (i.e., in unselected people who may or may not have the suspected disease).

The assessment of the analytical performance of tests carried out on CSF samples is complex because lumbar puncture is not usually repeated, CSF samples are limited in volume, and obtaining CSF samples from healthy controls is not easy. Moreover, results from routine CSF examination are not disease-specific [3]. Accordingly, account should be taken of the limitations of diagnostic sensitivity, specificity, and predictive values in the CSF area, as they are strongly influenced by the prevalence of diseases (Bayes theorem). For instance, in a laboratory that supports a neurology ward, the OCB predictive value for MS can be high, whereas in a general laboratory, which is likely to receive CSF samples from patients with infectious CNS diseases, the same value can be low. The general rule is therefore that CSF reports should be interpreted on the basis of diagnostic hypotheses. Table 1 reports the main pathological conditions for which CSF examination is indicated.

Table 1
Main clinical indications of lumbar puncture

Meningitis and meningoencephalitis
Multiple sclerosis and demyelinating encephalomyelitis
Dysimmune polyradiculoneuritis
Carcinomatous meningitis
Neurological involvement in systemic inflammatory/autoimmune diseases
CNS vasculitis
Devic's disease
Neurosarcoidosis
Pseudotumor cerebri
CT-negative, suspected subarachnoidal bleeding
Block of the CSF flow
Otorhinorrea
Creutzfeldt–Jacob's disease
Alzheimer's disease[a]

[a] Preliminary data indicate that the contemporary determination of CSF tau protein, hyperphosphorylated tau protein, and amyloid β_{1-42} are useful in the early diagnosis of the disease [4].

CSF examination plays a central role in the diagnosis of MS, especially in clinically isolated syndromes, and in primary progressive forms [5]. The previous consensus on CSF examination, which is ten years old, was indeed centred on MS [6]. This consensus did not deal thoroughly with the overall topic of procedure and method standardization. The main aim of the present report is to fill this gap (microbiological examination excluded). Two basic principles guided our work: a) a test is useful in clinical decision-making if, and only if, the results add new, clarifying information to the definition of clinical problems; and b) a new test should be cost-effective. Indeed, the effectiveness of a single test that is proposed for addition to a group of other tests should supplement the overall combination of diagnostic power and thus it conditionally derives added value from the independent value of the proposed test [7]. If, for instance, a new test's results enable the subgrouping of patients and if these subgroups are already obvious, or identifiable more cost-effectively by other methods, the new test may not be useful. The issue of cost-effectiveness as a criterion for the use of diagnostic tests and procedures is multifaceted, health-care system-dependent, and has only recently begun to receive consideration of appropriate scope and depth. OCB testing is a case in point: on the one hand, it could be said not to be cost-effective in MS; on the other hand, cost-effectiveness evaluation should allow for the reassurance value to patients of receiving a diagnostic test result, and the subsequent reduction of anxiety [8]. In the present paper, the expertise and knowledge of each participant in the standardization process compensated for the substantial lack of literature data on the topic.

The final document was the culmination of more than two years' drafting, mostly borne by email over two years. The points that compose the final document were discussed, and consensus on them reached, during two dedicated workshops; these took place in 2002 and 2003, and were run by the Italian Association of Neuroimmunology. Consensus for each point was based on a substantial majority.