

Diagnostic performances of biochemical tests for Multiple Sclerosis

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Introduction

Biochemical analyses performed on cerebrospinal fluid (CSF) have gained a relevant place in diagnostic work-up of Multiple Sclerosis (MS). In addition to the detection of oligoclonal bands (OCB) by isoelectric focusing (IEF), other assays (focused on intrathecal immune reaction) have received considerable attention (1). Aim of this work is to investigate the diagnostic performances (mainly focused on sensitivity) of such assays in a large population of patients.

Methods

400 patients were consecutively enrolled. They underwent lumbar puncture (LP) in their diagnostic work-up including CSF biochemistry and IEF from January 2014 to January 2019. The mean age was 48 ± 18 years. Diagnosis was prospectively collected by a blind neurologist, and compared with the initial suspicion. 127 patients (31,7%) were diagnosed of MS according to the 2017 McDonald criteria; 118 (29,5%) of other neurological inflammatory diseases (ID: inflammatory neuropathies, acute demyelinating encephalomyelitis, systemic autoimmune disorders with CNS involvement); 141 (35,2%) of non-inflammatory neurological diseases (NID: amyotrophic lateral sclerosis, dementia, non-inflammatory neuropathies, tumours). Patients with no detectable neurological disease (14, 3,5%) were excluded.

Results

For each parameter AUC, sensitivity and specificity are sequentially reported in Table I. KFLC index exhibits the highest values of both AUC and sensitivity, followed by KFLC/IgG ratio in CSF. This was true for the diagnosis of MS as well as for the occurrence of oligoclonal bands in CSF.

A very high correlation was evident between KFLC index and KFLC/IgG ratio in CSF and, as depicted in Fig. 1, most of patients with MS clustered in the right-upper region. On the other hand, although a rather good correlation, the same striking distribution of MS patients was not observed for the correlation between LFLC index and LFLC/IgG ratio in CSF.

When cut-off of 5 for KFLC index and 15 for KFLC/IgG ratio in CSF were employed, the diagnostic performances of the two indexes were roughly superimposable especially as concerning sensitivity and negative predicting value (Table II).

Conclusions

Of the assays investigated, KFLC index emerged as that with highest sensitivity, followed by the CSF KFLC/IgG ratio (2,3). IgG index (the so-called Link-index), still generally employed, showed a relatively low sensitivity.

Results confirm the strong diagnostic power of KFLC index. Since both serum and CSF are required to performed this test, a rather good alternative could be the CSF KFLC/IgG ratio, a parameter that can be easily applied on stored samples when serum is not available.

Table I: Sensitivity and Specificity of different parameters in predicting intrathecal synthesis and the presence of Multiple Sclerosis, calculated according the ROC curve

	Presence of OCB in CSF			Diagnosis of MS		
	AUC	Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)
KFLC, CSF	0.946	83.7	88.5	0.924	87.8	81.8
LFLC, CSF	0.745	59.3	74.2	0.729	60.8	70.9
IgG, CSF	0.641	68.1	53.1	0.630	68.9	51.0
KFLC/LFLC CSF	0.874	80.9	84.2	0.844	82.4	78.4
KFLC/IgG CSF	0.968	94.5	74.8	0.943	95.9	67.6
LFLC/IgG CSF	0.687	72.5	53.8	0.669	70.3	49.7
IgG index	0.853	75.8	77.9	0.845	79.7	73.6
KFLC index	0.981	97.8	77.9	0.955	98.7	70.1
LFLC index	0.837	86.8	60.8	0.842	90.0	56.8
KFLCi/LFLCi ratio	0.873	86.8	60.3	0.840	85.0	54.4

Fig.1: Correlation between (panel A) KFLC index and CSF KFLC/IgG ratio or (panel B) LFLC index and CSF LFLC/IgG ratio in patients with Multiple Sclerosis (●), Inflammatory Diseases (○) and non-Inflammatory Diseases (△)

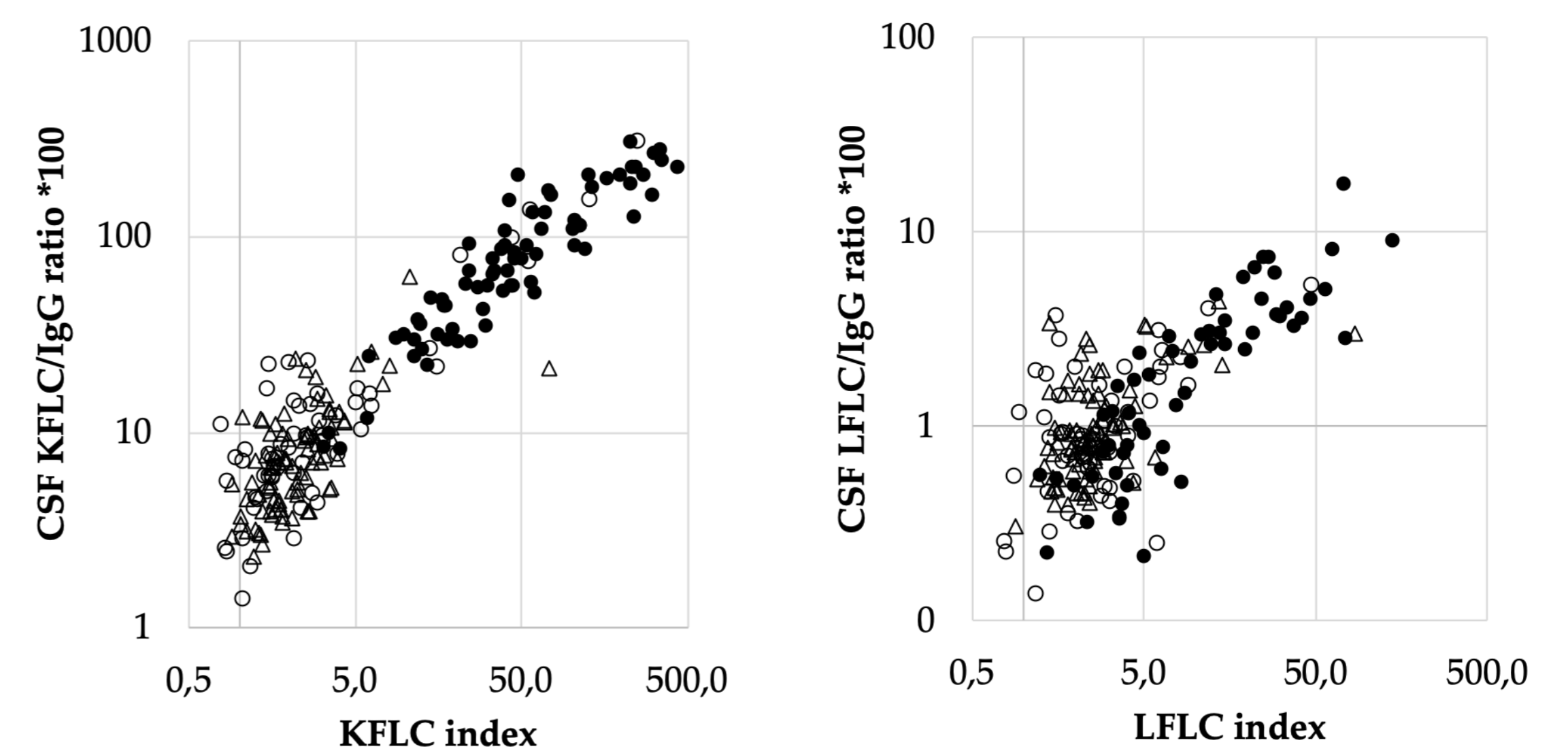


Table II: Performances of KFLC index and CSF KFLC/IgG ratio in diagnosing Multiple Sclerosis as derived from a Bayesian Calculator.

Parameter	KFLC index	KFLC/IgG ratio in CSF
Sensitivity (%)	95.327	93.458
Specificity (%)	81.633	77.871
Likelihood Ratio for a positive test	5.190	4.041
Likelihood Ratio for a negative test	0.057	0.085
Positive Predictive Value (%)	65.385	59.524
Negative Predictive Value (%)	97.959	96.996
Efficiency (%)	85.287	81.297
Pre test Probability (prevalence) (%)	26.683	26.683
Pre Test odds	0.364	0.364
Post Test odds	1.889	1.471
Post test Probability (%)	65.385	59.524
Number Needed to Diagnose (NND)	1.299	1.422

References

- 1) Ramsden DB. - Multiple sclerosis: assay of free immunoglobulin light chains. *Ann.Clin.Biochem.* 2017;54:5-13.
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- 3) Crespi I, Vecchio D, Serino R, Saliva E, Virgilio E, Sulas MG, Bellomo G, Dianzani U, Cantello R, Comi C. - K Index is a Reliable Marker of Intrathecal Synthesis, and an Alternative to IgG Index in Multiple Sclerosis Diagnostic Work-Up. *J Clin Med.* 2019 Apr 2;8(4). pii: E446. doi: 10.3390/jcm8040446.