Research Paper

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kFLC Index: a novel approach in early diagnosis of Multiple Sclerosis

Medical Science

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ABSTRACT

The recent application of nephelometric assay to determinate free light chains (FLCs) in cerebrospinal fluid (CSF) makes it possible the use of this test in clinical routine to support diagnostic procedures in multiple sclerosis (MS). We measured kappa FLCs (kFLCs) and Albumin in CSF and serum, using a nephelometric assay, in a MS patient who underwent lumbar puncture for diagnostic purposes and we calculated the kFLC Index. Our observation suggests that an altered kFLC Index may improve the accuracy of the current criteria for MS diagnosis. kFLC Index may be an early predictive factor to improve diagnosis, prognosis and to monitor response to therapy.

INTRODUCTION

Immunoglobulin G (IgG) intrathecal synthesis is one of the main immunologic abnormalities in Multiple Sclerosis (MS). IgG abnormal synthesis might be detected using IgG oligoclonal bands (Andersson et al., 1994) (OCBs), IgG indices (Link, Reiber) and determination of free light chains (FLCs) in cerebrospinal fluid (CSF) and serum. Plasma cells produce FLCs in excess in serum and CSF when compared to the heavy chains; furthermore in CSF they do not undergo renal clearance and FLCs interference from simple passage of barrier is minimal, due to their low concentration in serum (Fischer, Arneth, Koehler, Lotz, & Lackner, 2004).

Several MS studies have detected FLCs in CSF and have shown that free kappa light chains might be suitable for the detection of intrathecal immunoglobulin synthesis (Desplat-Jego et al., 2005; Fischer et al., 2004; Jenkins, Cheng, & Ratnaike, 2001). OCBs continue to be the gold standard for the diagnosis of intrathecal immunoglobulin synthesis but recently the nephelometric and ELISA FLCs determination is comparable with OCBs (Desplat-Jego et al., 2005; Fischer et al., 2004; Petzold, 2013; Senel et al., 2014).

An even higher sensitivity of kappa light chains compared with OCBs has recently been discussed in Multiple Sclerosis (Duranti et al., 2013); whereby FLCs determination could became a promising biomarker to highlight intrathecal IgG synthesis (Laman, Thompson, & Kappos, 1998).

Severity and disease progression of MS are extremely variable among patients, and identifying reliable markers of disease activity in MS might be useful to improve diagnosis, prognosis and to monitor response to therapy.

CASE STUDY

During our study (Duranti et al., 2013), we had a special case: a healthy 28 years old Italian woman suddenly manifested left upper limb hypoesthesia in October 2012. On first admission to the hospital, she underwent neurological examination, blood and urinary standard tests, lumbar puncture (LP), brain and spinal cord magnetic resonance imaging (MRI) with gadolinium. Blood and urinary analysis were normal. CSF analysis revealed negative IgG index, borderline oligoclonal IgG expression, one OCBs and increased kFLCs Index (Table 1, 1 LP). OCBs were determined by immunofixation (Hydragel9 CSF Isofocusing; Sebia) on a semi-automated agarose electrophoresis system (Sebia Hydrasys).

Immunoglobulin, albumin and kFLCs concentrations were measured by nephelometry (BN Prospec, Siemens, Germany) in fresh CSF and serum samples. Quantitative determination of kFLCs was performed with the N Latex FLCs kappa Kit that uses monoclonal antibodies (Siemens).

The use of kFLCs Index calculated as $\frac{kFLC_{CSF}}{kFLC_{Serum}} / \frac{Albumin_{CSF}}{Albumin_{Serum}} \times 1000$ which takes into account the function of the blood–CSF barrier increases the diagnostic accuracy of kFLCs determination. The patient showed a value of kFLCs Index of 26,64, significantly positive compared to cut-off ≤ 12, as determined in our previous paper (Duranti et al., 2013).

Magnetic resonance imaging showed a demyelinating leukoencephalopathy without signs of disease activity (Figure 1a). She was discharged four days after hospital admission with the diagnosis of clinically isolated syndrome (CIS).

Five months later, the patient developed a lower extremity

hyposthenia. CSF and serum test showed the presence of six oligoclonal bands and a kFLCs Index value of 154 (Table 1, 2 LP).

She repeated brain and spinal cord MRI that showed increased lesion load (Figure 1b). The diagnosis of Multiple Sclerosis was made. Currently the patient is enrolled in a clinical trial; she had no more relapses or new lesions on MRI.

DISCUSSION

Diagnostic criteria for Multiple Sclerosis include clinical and radiological assessments to demonstrate the dissemination of lesions in space (DIS) and time (DIT) (Polman et al., 2011). Although to date the diagnosis can be made only on clinical and radiological data, evidence of intrathecal immunoglobulin synthesis is still important to exclude alternative diagnoses (Palace, 2009) and it is considered a risk factor for conversion to definite MS (CDMS).

Our hypothesis is that kFLCs Index may be an early marker and may support the diagnosis of MS better than other CSF tests. The utility of kFLCss to detect intrathecal immunoglobulin synthesis has been previously reported by other research groups, but their use in clinical practice was limited, as FLCs determination is a technically challenging task with routine methods. Nowadays, FLCs can be dosed with an automatic, reliable, and operator independent nephelometric assay, able to provide results in a short time, with advantage for both the patient and the clinician.

Considering the kFLCs Index cut-off established in our previous study (Duranti et al., 2013) together with other findings from several published reports on intrathecal immunoglobulin synthesis (Fischer et al., 2004; Jenkins et al., 2001), we can conclude that the kFLCs Index seems to be an earlier marker of MS, and its use in clinical routine may help the clinician in potential prognostic assessments. Results from different time points (CIS phase; MS -onset phase; MS -stable phase) should be compared in future studies to see whether kFLCs quantification could be used to monitor the MS progression.

Conflict of interest statement

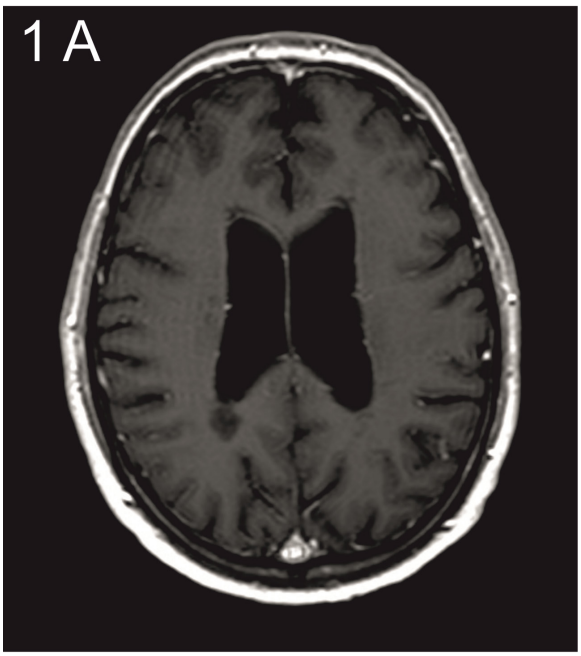
All authors report no conflict of interest.

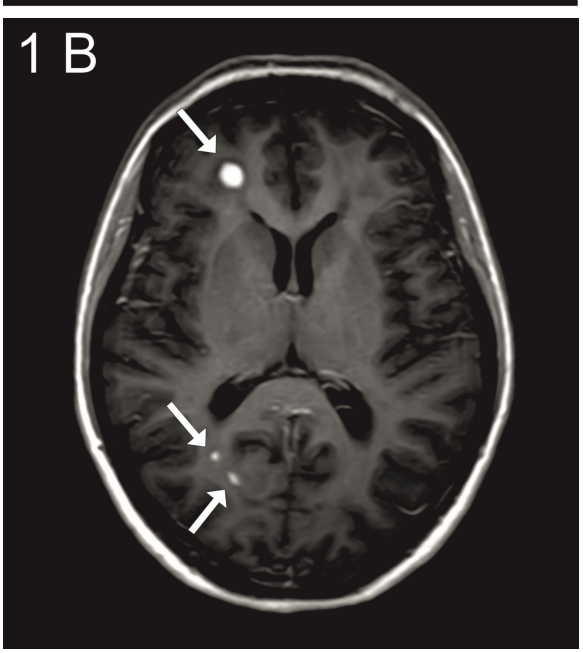
Table 1. Patient characteristics on first admission to the hospital and on the second Lombar Puncture (LP).

Patient	Age (years)	Sex	Qalb	IgG Index				OCBs
1 LP	28	F	4.6	0.45	0.97	0.12	26,64	1
2 LP	28	F	6.4	0,91	2.3	2.4	154	6

Figure legend

Figure1. MRI (T1 with gadolinium; axial view) findings of patients 1 in CIS stage (a) and after five months in definite MS stage (b). The arrows indicate the lesions, showing an increased load than before.





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