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## Brief communication

# Tear analysis as a tool to detect oligoclonal bands in radiologically isolated syndrome



## L'analyse des larmes permet de détecter les bandes oligoclonales dans le syndrome radiologiquement isolé

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### ABSTRACT

**Background.** – Although radiologically isolated syndrome (RIS) is a newly defined entity, incidental findings of T2 hypersignals on brain MRI can lead to misdiagnosis or useless investigations. The detection of oligoclonal bands (OCBs) in cerebrospinal fluid (CSF) is a major indicator that helps in diagnosis of subclinical inflammatory disease of the central nervous system, but lumbar puncture still remains an invasive option.

**Methods.** – We have prospectively included patients with RIS, have compared the results of CSF and tear OCB detection by isoelectric focusing (IEF) and assessed concordance between OCB detection in tears and in CSF. Tears were collected using a Schirmer strip.

**Results.** – In 45 recruited RIS patients, OCBs were detected in CSF for 55% (25/45) and in tears for 50% (21/42) of samples.

**Conclusions.** – We suggest that tear OCB detection may replace CSF OCB detection as a diagnostic tool in patients with RIS and be useful in follow-up.

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### R É S U M É

#### Mots clés :

Liquide céphalorachidien  
 Syndrome radiologiquement isolé

**Introduction.** – La description et la publication des critères diagnostiques du syndrome radiologiquement isolé sont récentes. La découverte fortuite d'anomalies de signal hyper-intenses sur les séquences T2 d'une IRM cérébrale ou médullaire peut conduire à

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Sclérose en plaques  
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Critères diagnostiques

des explorations inutiles ou à des erreurs diagnostiques. La détection de bandes oligoclonales dans le liquide céphalorachidien est un marqueur important pour le diagnostic d'une affection démyélinisante du système nerveux central de l'adulte. Dans le cadre du bilan étiologique d'anomalies de la substance blanche de découverte fortuite, la ponction lombaire peut être considérée comme un geste invasif.

*Méthodes.* – Nous avons inclus prospectivement des patients présentant un RIS et avons comparé la présence de bandes oligoclonales en isofocalisation dans les larmes et le liquide céphalorachidien. Les larmes étaient recueillies dans les 2 yeux avec une bandelette de papier utilisée dans le test de Shirmer.

*Résultats.* – Quarante-cinq patients présentant un RIS ont été inclus. Les bandes oligoclonales ont été détectées chez 55 % des patients (25/45) dans le LCR et 50 % des larmes (21/42). Les difficultés principales étaient essentiellement l'absence de larmes chez certains patients ou la dilution trop importante des larmes sur la bandelette au moment du recueil.

*Conclusion.* – Nous suggérons que l'analyse des larmes dans le RIS peut être un outil diagnostique utile par la détection de bandes oligoclonales et facilement reproductible pour le suivi en cas de négativité.

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## 1. Introduction

Radiologically isolated syndrome (RIS) is a recently defined entity that describes the incidental discovery of lesions suggestive of multiple sclerosis (MS) on brain magnetic resonance imaging (MRI), with demonstration of dissemination in space without symptom expression, with a normal neurological examination, and no better medical explanation to account for the observed anomalies. In RIS, the detection of oligoclonal bands (OCBs) in cerebrospinal fluid (CSF) is supportive for space dissemination validation associated with MRI multiple sclerosis (MS) diagnostic criteria, as published by Barkhof et al. [1]. It gives strength to RIS diagnosis compared with other incidental white matter T2 lesions. However, lumbar puncture for CSF collection is considered relatively invasive. Previous studies have demonstrated interest of OCB detection in CSF to the diagnosis of MS and CIS and applicability in tears [2–4].

## 2. Materials and methods

All participating subjects met strict entry criteria for RIS as defined previously [5]. T2 hyperintensities have to meet specific MRI criteria in shape, location and number with no better account for another disease process. Patients were considered as having RIS if they met radiological criteria and have no clinical symptoms consistent with neurologic dysfunctions. Patients underwent annual clinical assessment, brain and spinal MRI scans as part of an observational, prospective, multi-center, longitudinal study protocol that included 3 recruiting sites specialized in central nervous system (CNS) inflammatory diseases in France [6]. All participants gave their informed consent and were asked for a screening diagnosis. At baseline, all RIS patients had paraclinical analyses (CSF, visual evoked potentials – VEP, spinal MRI) and biological screening (serological panel, anti-nuclear and antiphospholipid antibodies). According to

French national regulations (CNIL), EDMUS databases were declared and no additional approval was specifically needed from the ethics committee or institutional board for this kind of descriptive study. Even if RIS patients are not classified as multiple sclerosis, the OFSEP scientific committee has recognized in 2013 the French RIS cohort as a priority work. Since, data are collected in EDMUS software and informations were analyzed anonymously. Regarding this specific work, only two centers were able to gather their patients as a pilot analysis for tears study.

A total of 45 consecutive RIS subjects were enrolled for the specific tears analysis. The objective was to study the relationship between tears/CSF isoelectric focusing (IEF) profiles. Tears were collected using a Schirmer strip placed in the external cul-de-sac of each inferior eyelid. Collected tears volume did not exceed one to two graduations (5–10  $\mu$ l). The dry end of the Schirmer strip was cut, and the sample was placed in a test tube (to avoid humidification by ambient air). Ten to 15 CSF drops were collected in a dry tube by classical lumbar puncture. At the same time, a blood sample (2 ml) was collected from each patient into a dry tube, which was then centrifuged at 3000 rpm for 15 minutes in to obtain the serum. Samples were mailed to a single laboratory, which performed all the analyses. Quantification of IgG levels in CSF and serum was performed as previously described [4]. Tears were rehydrated with 50 ml of isotonic saline solution and 10 ml were picked up and loaded onto agarose gel without standardizing IgG levels. Membranes were subsequently immunoblotted by blocking proteins (bovine milk proteins), followed by incubation with a peroxidase-conjugated goat anti-human-IgG serum. Finally, membrane signals were developed with chromophore and air-dried. The presence of at least three OCBs was required for a positive result. Non-interpretable samples were excluded. The technical difficulty of assessing the presence or absence of OCBs on nitrocellulose membranes after immuno-blotting, because of its photosensitivity, represents a shortcoming tears analysis because results should be read quickly using incidental light. Univariate analysis was performed with SPSS 20.0 software for Mac OS X.

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