Cytokine 111 (2018) 140–145

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Short communication

# Elevated soluble syndecan-1 levels in neuromyelitis optica are associated with disease severity

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ARTICLE INFO

*Keywords:*
Cerebrospinal fluid
Soluble syndecan-1
Neuromyelitis optica
Multiple sclerosis
Disease severity

ABSTRACT

Syndecan-1 (SDC-1) is a transmembrane member that has a profound influence on the resolution of inflammation. Soluble syndecan-1 (sSDC-1) levels have been shown to increase in many inflammatory diseases. However, it remains unknown whether sSDC-1 concentration is elevated in neuromyelitis optica (NMO) and multiple sclerosis (MS) patients. The aims of this pilot study were to investigate the relationship between sSDC-1 and disease severity in NMO and MS and whether sSDC-1 has potential as an effective marker for disease severity. We measured sSDC-1 concentrations by using an enzyme-linked immunosorbent assay (ELISA). NMO patients had significantly higher CSF sSDC-1 levels than MS patients or controls. We also found a positive correlation between the increased CSF sSDC-1 levels and increased severity in NMO disease, but not in MS. In NMO, CSF sSDC-1 concentrations were positively correlated with CSF interleukin (IL)-6, IL-8 and IL-17. Overall, we showed levels of CSF sSDC-1 were higher in NMO patients and had a positive relationship with disease severity of NMO but not with MS. CSF sSDC-1 may be an effective marker of NMO disease severity.

## 1. Introduction

NMO and MS are two typical immune-mediated inflammatory demyelinating diseases of the central nervous system. NMO was regarded as a variant of MS until the water channel anti-aquaporin-4 (AQP4) antibodies were discovered. Moreover, differences between MS and NMO such as clinical characteristics, pathology, neuroimaging results, and response to some immunotherapies distinguish these diseases [1]. Many pro-inflammatory and anti-inflammatory cytokines and chemokines contribute to NMO pathogenesis and NMO severity can be regulated by the balance between these opposing factors [2,3].

Syndecan-1 (SDC-1) is a transmembrane HSPG that consists of three different domains (cytoplasmic, transmembrane, and extracellular) and predominantly expressed by epithelial cells and plasmacytes [4]. The main function of SDC-1 in adult mammals is to resolve inflammation. SDC-1 deficiency has been proved to be involved in many diseases with uncontrolled inflammation in vivo and vitro [5]. SDC-1 also takes part in wound healing, fibrosis, tumor biology, and infectious diseases [4].

Through ectodomain shedding, the syndecan extracellular domain can be proteolytically released from the cell surface to become a soluble HSPG. This process can be induced by matrix metalloproteinases (MMPs) [6]. In NMO, proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 are upregulated [2,3,7] and induce MMPs [6–9]. Moreover, soluble SDC-1 (sSDC-1) is increased by shedding during inflammation and correspondingly membrane bound SDC-1 decreased [4]. The current observations suggest that syndecan-1 shedding has distinct regulatory functions in different inflammatory diseases. For example, syndecan-1 shedding functions as an anti-inflammatory molecule in allergic lung inflammation but an pro-inflammatory molecule in bleomycin-induced acute lung injury by inducing an CXC chemokine gradient mobilization that guides transepithelial efflux of neutrophils [8]. However, the role of sSDC-1 in NMO and MS remains unknown. This pilot study investigated the serum and cerebrospinal fluid (CSF) concentrations of sSDC-1 in NMO and MS patients and explored its role in the pathogenesis of NMO.

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https://doi.org/10.1016/j.cyto.2018.08.017
Received 5 May 2018; Received in revised form 27 July 2018; Accepted 15 August 2018

**Table 1**
Demographic and clinical features of patients and controls.

| | NMO | MS | Control |
|---|---|---|---|
| No. of subjects (n) | 23 | 12 | 16 |
| Gender (female/male) | 15/8 | 5/7 | 11/5 |
| Age (years) | 33.43(16–60) | 34.58(15–52) | 33.88(27–39) |
| Disease duration (years) | 2.24(1–4) | 1.75(1–2) | – |
| EDSS scores | 4.22(2–6.5) | 2.25(1–3.5) | – |
| *NMO-IgG* | | | |
| Positive | 19 | – | – |
| Negative | 4 | – | – |

Disease duration (years) refers to years from disease onset to sampling.
EDSS, Expanded Disability Status Scale; NMO, neuromyelitis optica; MS, multiple sclerosis.

## 2. Patients and methods

### 2.1. Patients and controls

23 NMO patients, 12 MS patients and 16 controls with noninflammatory neurological diseases were enrolled. This study was approved by the Ethics Committee of the Nan Fang Hospital of the Southern Medical University. Each enrolled participant signed informed consent. Table 1 shows the demographic and clinical features of the patients.

### 2.2. Preparation of blood and CSF samples

After sampling, we immediately centrifuged all samples to eliminate cells and other insoluble materials and then distributed equal aliquots into polypropylene tubes for storage at −80 °C until assay.

### 2.3. Study of serum and CSF samples

sSDC-1 levels were measured via a commercially available ELISA kit (Diaclone, Besancon, France) according to the manufacturer's instructions.

### 2.4. Statistical analysis

For CSF sSDC-1, serum sSDC-1, IL-6, IL-8 and IL-17, data were presented as mean ± standard deviation or median with range for age, disease duration and EDSS score. The Kruskal-Wallis tests and Spearman's test were used for the comparison between groups and determining the correlations between sSDC-1 levels and proinflammatory cytokines as well as aquaporin-4 antibodies levels respectively. P-values $< 0.05$ were considered statistically significant. SPSS 20.0 software was used to perform statistical analyses. Receiver operating characteristic (ROC) curve were performed using GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA, USA). Power analysis were analyzed using BMDP Statistical Software (1993), the following was found: With the proposed sample size of 23 NMO patients and 16 controls, the study will have power of 98.78% to yield a statistically significant result.

## 3. Results

### 3.1. CSF and serum sSDC-1 in MS and NMO patients and controls

The mean plasma sSDC-1 (ng/ml) concentrations for NMO, MS and controls were 99.97 ± 87.25, 74.79 ± 25.98 and 59.61 ± 23.58, respectively. Differences in serum sSDC-1 levels between three groups did not reach statistical significance (Fig. 1A). CSF sSDC-1 levels were significantly higher in the NMO compared with MS and controls (MS, 13.44 ± 6.97 vs 8.19 ± 4.53 ng/ml, $p = 0.013$; controls,13.44 ± 6.97 vs 5.71 ± 1.79, $p < 0.001$). The CSF sSDC-1 levels were not significantly different between MS patients and controls ($p = 0.189$)

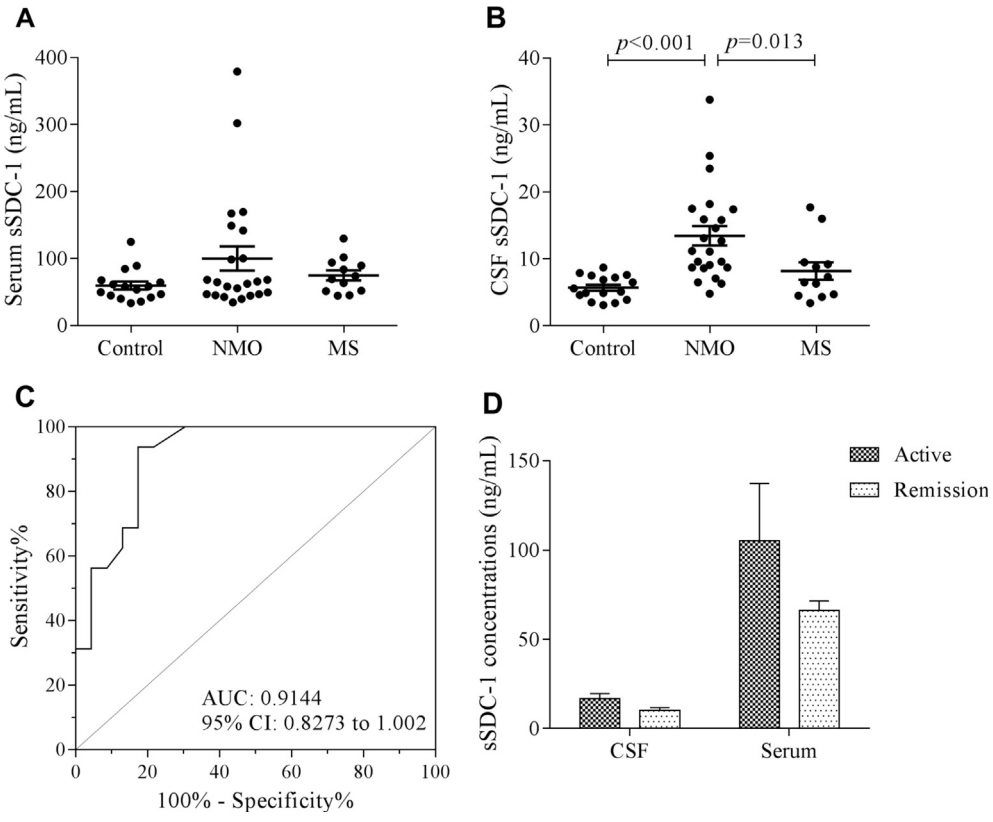


**Fig. 1.** Comparison of serum and CSF sSDC-1 levels (A, B). (A) No difference was found in serum sSDC-1 levels between NMO, MS and controls. (B) CSF sSDC-1 levels were higher in the NMO compared with MS and controls (MS, $p < 0.001$; CTLs, $p = 0.013$). Diagnostic values of sSDC-1 for the assessment of disease activity (C). The 95% confidence interval is from 0.8273 to 1.002. The area under the ROC curve is 0.9144. Comparison of CSF and serum sSDC-1 levels in active and remission periods in NMO (D). In NMO, both serum and CSF soluble SDC-1 levels were significantly higher in the relapse than in remission (CSF, $p = 0.013$; serum, $p = 0.014$).