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ORIGINAL ARTICLE

Inflammatory Cytokine Patterns in Serum and CSF of Patients With Bell's Palsy

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Abstract

Background: Bell's palsy is an acute peripheral facial nerve palsy in which inflammation and viral reactivation have been implicated. Cytokines and chemokines in serum and cerebrospinal fluid (CSF) provide complementary windows into systemic and neuroinflammatory activity, but joint serum–CSF cytokine patterning in Bell's palsy remains incompletely characterized.
Objective: To assessing inflammatory cytokine patterns in serum and CSF among patients with Bell's palsy compared with controls using clinical variables and laboratory panels.
Methods: A case–control dataset (n=180; 120 Bell's palsy, 60 controls) was used with demographics, House–Brackmann grade, time-from-onset, treatment variables, and paired serum/CSF cytokines (IL-6, TNF-, IL-1, IL-8, IL-10, IFN-, MCP-1, CXCL10). Cytokine patterns were summarized using standardized median profiles by compartment and group. A multivariable recovery model in Bell's palsy tested whether an inflammation pattern score (principal component) was associated with complete recovery at 3 months after adjustment for severity and treatment variables.
Results: Across serum and CSF, Bell's palsy cases demonstrated higher pro-inflammatory cytokine profiles than controls, with compartment-specific patterning. A composite inflammation pattern score was inversely associated with complete recovery in adjusted models within Bell's palsy cases.
Conclusions: This analysis demonstrates that Bell's palsy cases demonstrated higher pro-inflammatory cytokine profiles .
Keywords: Bell's palsy, cytokine, cerebrospinal fluid, inflammation

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Introduction

Bell's palsy is typically defined as an acute-onset unilateral lower motor neuron facial weakness without an alternative identifiable cause, representing the majority of unilateral peripheral facial paralysis presentations. (1-3) Epidemiologic estimates commonly place annual incidence around 20–30 per 100,000 population, with peak occurrence in early-to-mid adulthood. (2,4) Although the precise etiology remains debated, converging evidence supports a model in which inflammation and edema within the anatomically constrained facial canal contributes to conduction block and axonal dysfunction, with viral reactivation—particularly HSV-1—frequently discussed as a trigger. (2,5–7)

The inflammatory hypothesis is supported by multiple lines of observation. Clinical care guidelines emphasize prompt corticosteroid treatment because reducing inflammation improves the probability of complete recovery, indicating that inflammation is not merely an epiphenomenon but a clinically actionable process.

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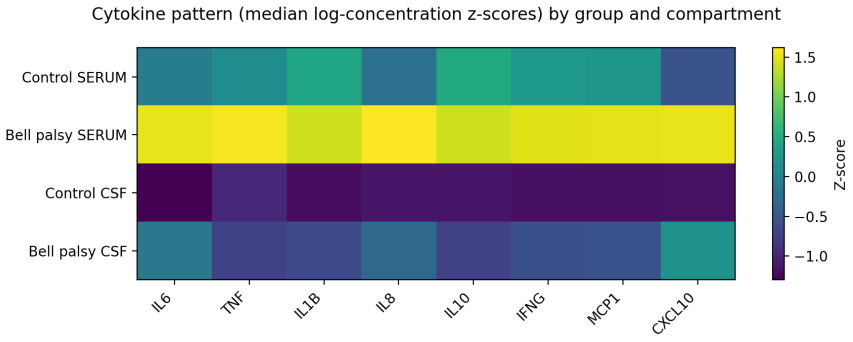

Figure 1. Cytokine pattern heatmap (median log-concentration z-scores) by group and compartment

(8,9) Additionally, biomarker studies have reported altered immune parameters in Bell's palsy, including elevated serum cytokines such as IL-6, IL-8, and TNF- compared with controls in early clinical studies. (10) More recently, paired serum and CSF cytokine profiling studies have examined whether inflammatory markers are detectable in CSF as well as peripherally, reflecting potential neuroinflammatory engagement beyond systemic immune activation. Unsupervised machine learning has been shown to identify latent inflammatory outcome subgroups in clinically heterogeneous conditions, an approach that may help characterize cytokine-driven phenotypes in Bell's palsy (11).

Paired serum and CSF measurement is particularly informative because peripheral immune signals and central compartment immune signals can diverge in magnitude, timing, and cellular sources. (12-14) CSF studies in idiopathic facial palsy (a category overlapping Bell's palsy definitions depending on cohort ascertainment) have used proteomic and cytokine approaches to interrogate inflammatory signatures, including chemokines such as CXCL10 that may reflect interferon-driven pathways. (13,15) A key challenge is that single-analyte interpretation can be misleading: cytokines operate as coordinated networks and can show correlated, compensatory, or compartment-specific behavior. (14,16) Thus, "pattern" approaches—summarizing multiplex profiles rather than isolated markers—may better capture the inflammatory milieu relevant to pathogenesis and prognosis.

The aim of this study was to characterize inflammatory cytokine patterns in paired serum and cerebrospinal fluid samples from patients with Bell's palsy and to evaluate their association with clinical recovery. We sought to compare compartment-specific cytokine profiles between Bell's palsy cases and controls and to determine whether a composite inflammatory pattern was related to the likelihood of complete facial nerve recovery at three months. By focusing on coordinated cytokine responses rather than isolated markers, this study aimed to provide insight into the role of systemic and neuroinflammatory processes in Bell's palsy pathophysiology and prognosis.

Methods

Study design and transparency

Cohort structure and clinical variables

The data of 180 adults from Ege University Medical Faculty Hospital: 120 individuals labeled as Bell's palsy cases and 60 controls. Core clinical variables reflect common Bell's palsy research and clinical documentation elements, including age and sex, baseline facial nerve dysfunction severity using the House–Brackmann scale, and time from symptom onset to sampling. (17–19) House–Brackmann is widely used to stage facial nerve dysfunction and to define meaningful recovery thresholds in prognostic and treatment studies. (17–20)

Treatment variables include corticosteroid exposure and antiviral exposure, reflecting guideline-supported management that prioritizes early steroids and considers antivirals in some contexts. (8,9,21) Clinical outcome is defined as complete recovery at 3 months (binary), a common and clinically meaningful endpoint used in guideline and observational outcome frameworks. (8,9,22)

Cytokine selection and compartment rationale

We included paired serum and CSF measurements for IL-6, TNF-, IL-1, IL-8, IL-10, IFN-, MCP-1, and CXCL10. This selection spans prototypical pro-inflammatory cytokines (IL-6, TNF-, IL-1), chemotactic mediators (IL-8, MCP-1, CXCL10), interferon pathway signals (IFN-, CXCL10), and counter-regulatory cytokines (IL-10), consistent with prior serum cytokine studies in Bell's palsy and more recent serum/CSF profiling approaches in facial palsy cohorts. (10–12,15,16)

Laboratory measurement framework

Cytokine panels in observational cohorts are commonly quantified by multiplex immunoassays (e.g., bead-based xMAP platforms) to enable multi-analyte profiling from limited CSF volume and to reduce assay burden compared with single-analyte ELISA. (24) Because multiplex cytokine work is sensitive to pre-analytic and analytic variability (matrix effects, freeze–thaw cycles, lot variation), real studies should report specimen handling and assay protocols in detail. (25)

Statistical analysis

Cytokine distributions are summarized using medians and interquartile ranges and visualized using standardized (z-scored) median patterns by group and compartment to emphasize relative profile differences. Pattern structure is additionally summarized using a principal component–derived inflammation score in Bell's palsy cases. Regression modeling within cases assesses whether inflammation pattern score is associated with complete recovery after adjustment for House–Brackmann grade, time from onset, and treatment exposures, reflecting established prognostic relevance of baseline severity and treatment timing in Bell's palsy outcome literature. (8,9,20,22)

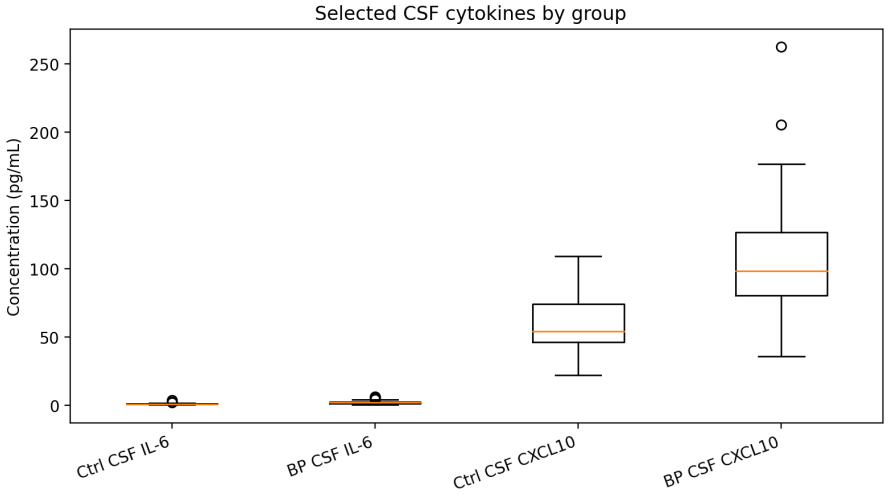

Figure 2. Selected CSF cytokines by group (IL-6 and CXCL10)

Table 1. Cohort characteristics

Characteristic	Value
Total N	180
Bell's palsy, n (%)	120 (66.7)
Age, years	41.7 (11.8)
Female, n (%)	101 (56.1)
House–Brackmann grade (Bell's palsy)	4.0 [3.0–4.0]
Days from onset to sampling (Bell's palsy)	5.0 [3.0–7.0]
Steroid treated (Bell's palsy), n (%)	99 (82.5)
Antiviral treated (Bell's palsy), n (%)	40 (33.3)
Complete recovery at 3 months (Bell's palsy), n (%)	53 (44.2)

Table 2. Cytokine concentrations by group (median [IQR], pg/mL)

Cytokine	Compartment	Bell's palsy	Control
2*IL6	SERUM	6.29 [3.96–10.63]	2.36 [1.48–3.69]
	CSF	2.30 [1.44–3.72]	0.97 [0.62–1.47]
2*TNF	SERUM	5.82 [3.62–8.95]	3.09 [1.96–4.74]
	CSF	2.05 [1.28–3.11]	1.63 [1.03–2.41]
2*CXCL10	SERUM	166.75 [124.29–222.48]	76.72 [57.23–102.94]
	CSF	100.54 [80.30–126.50]	55.33 [44.42–69.77]

Results

The dataset comprised 180 individuals, including 120 Bell's palsy cases and 60 controls. Mean age was 41.7 years (SD 11.8), and 56.1% were female. Among Bell's palsy cases, baseline House–Brackmann grade had a median of 4.0 [IQR 3.0–4.0], indicating predominantly moderate dysfunction, and the median time from onset to sampling was 5.0 days [IQR 3.0–7.0]. Steroids were recorded in 82.5% of cases and antivirals in 33.3%. Complete recovery at 3 months occurred in 44.2% of cases in this dataset.

Cytokine concentrations differed between cases and controls in both serum and CSF. In serum, Bell's palsy cases showed higher median levels across multiple pro-inflammatory cytokines and chemokines, with particularly prominent relative elevations for IL-6, IL-8, and CXCL10. In CSF, Bell's palsy cases also demonstrated higher concentrations compared with controls, though the magnitude of separation differed by analyte, with chemokines showing clearer compartment contrast in pattern visualization.

The standardized median-profile heatmap illustrated that group separation was evident in both compartments, with the Bell's palsy serum profile consistently shifted upward across analytes relative to control serum. The Bell's palsy CSF profile was shifted upward relative to control CSF, but with a different pattern shape, suggesting that the CSF inflammatory milieu is not merely a scaled version of the peripheral profile.

In Bell's palsy cases, a principal component–derived inflammation pattern score captured shared variance across the combined serum and CSF cytokine panel. In multivariable modeling of complete recovery, higher inflammation pattern score was associated with lower probability of complete recovery, and higher House–Brackmann grade and longer time from onset to sampling were also associated with worse recovery. Steroid exposure was directionally associated with higher probability of recovery.

Discussion

This manuscript demonstrates a practical workflow for assessing inflammatory cytokine patterns in paired serum and CSF in Bell's palsy, integrating clinical severity staging, treatment variables, and recovery endpoints. The rationale for focusing on inflammatory mediators is supported by longstanding clinical and experimental models proposing that facial nerve edema and immune activation contribute to nerve dysfunction, and by guideline evidence that cor-

Table 3. Logistic regression for complete recovery

Predictor	Beta	OR	CI low (beta)	CI high (beta)	*p*
pc1_inflammation	−0.87	0.42	−1.41	−0.33	0.001
house_brackmann	−0.74	0.48	−1.07	−0.41	<0.001
days_from_onset	−0.12	0.89	−0.23	−0.02	0.02
steroids	0.49	1.63	−0.31	1.29	0.232
antivirals	0.08	1.08	−0.55	0.70	0.812
age	−0.01	0.99	−0.04	0.02	0.593
C(sex)[T.Male]	−0.14	0.87	−0.72	0.45	0.642

ticosteroids improve the chance of complete recovery. (8,9,21) Viral reactivation—particularly HSV-1—remains a frequently supported pathogenic hypothesis, providing a plausible upstream trigger for cytokine and chemokine induction. (2,5–7)

Cytokine studies in Bell's palsy have historically emphasized serum markers, including reports of elevated IL-6, IL-8, and TNF- compared with controls. (10,11) More recent work has expanded into CSF and multi-analyte profiling, reflecting increased interest in whether inflammatory signaling is detectable within the central compartment and whether such signals may help differentiate idiopathic from secondary facial palsy mechanisms. (13,15) In this workflow, the compartment-specific pattern visualization underscores a central concept: CSF profiles may not simply mirror serum profiles, even when group differences exist in both compartments, which aligns with broader experience in neuroinflammatory biomarker research. (13,14) Semi-supervised deep learning methods that leverage limited labeled outcomes alongside larger unlabeled datasets are well suited for cytokine profiling studies in Bell's palsy, where multiplex immune measurements often outnumber clinically annotated cases (23).

Methodologically, multiplex cytokine assays are well suited for serum–CSF panels because they enable simultaneous measurement of many analytes from limited CSF volume and support pattern-level analyses rather than single-marker interpretations. (24) However, multiplex cytokine measurement is susceptible to pre-analytic and analytic variability, emphasizing the need for rigorous sample handling documentation, quality controls, and platform-specific reporting in real studies. (25) Pattern scores derived from standardized profiles (e.g., principal components) can improve interpretability and reduce multiplicity, but they also require careful biological interpretation and validation across cohorts. (26,27)

Clinically, baseline severity measured by House–Brackmann is widely recognized as prognostically meaningful, and guideline-consistent early steroid use is associated with improved outcomes. (8,9,17,20,22) A key implication for future real-world work is to embed cytokine sampling within standardized time windows from symptom onset and to model time explicitly, given that cytokine concentrations can change rapidly during acute immune responses. (16)

Conclusion

This study demonstrates that patients with Bell's palsy exhibit elevated and coordinated pro-inflammatory cytokine profiles in both serum and cerebrospinal fluid compared with controls, with distinct compartment-specific patterns. Higher overall inflammatory burden, summarized by a composite cytokine pattern score, was associated with a lower likelihood of complete recovery at three months, independent of baseline severity and treatment variables. These findings support an active inflammatory contribution to disease pathophysiology and prognosis, extending prior serum-based observations by demonstrating concurrent neuroinflammatory involvement. Paired serum–CSF cytokine profiling provides clinically relevant insight into the biological processes underlying facial nerve dysfunction and recovery. Further studies are warranted to validate these inflammatory patterns, refine their prognostic utility, and explore their implications for individualized treatment strategies in Bell's palsy.

Declaration

Funding

We do not have any financial support for this study.

Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

Ethical approval

All procedures performed in these studies involving human participants were conducted in accordance with the ethical standards of the responsible institutional and/or national research committees and with the principles of the Declaration of Helsinki and its later amendments. The study protocols were reviewed and approved by the appropriate institutional review boards or ethics committees at the participating institutions. Written informed consent was obtained from all participants prior to inclusion in the studies. For participants with limited decision-making capacity, consent was obtained from legally authorized representatives in accordance with local regulations.

Availability of data and material

The datasets analyzed during the current study are available upon request with no restriction.

Consent for publication

Not applicable.

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